With respect to '313 the Examiner claims that the broad release rates have been taught in this reference and that the dissolution rates in Applicant's claims are overlapped by the '313 Patent. The Examiner admits, however, that "... EPA '313 does not disclose the exact release rates claimed by Applicant..." (bottom of page 1, top of page 2).

The determination of the dissolution rates in '313 is in accordance with U.S. Pharmacopoeia XXI in 0.05M KCl at pH 7.0 (not in accordance with Applicant's claimed procedure).

Additionally, Applicant's claims further include a Cmax in the blood plasma at a Tmax of between about 10-15 hours. In Applicant's previous response, Applicant asserted that '313 does not teach Applicant's claimed formulations and methods. In support of Applicant's position, Applicant directed the Examiner to example 14 based on example 1 which has a Cmax of 5 hours. (See Figure 2a). Example 14 states the formulation of Example 1 is suitable for once daily administration given the Tmax of 14 hours (page 20, lines 33-34). However, Figure 2(a) shows otherwise (Tmax of 5 hours).

The Examiner has now responded that Applicant's release rates overlap ('313 and Applicant's claims) and that the Pharmacological Data for what appears to be a single dose of the Example 4 formulation gives a Cmax at a Tmax of 13 hours (See page 24, line 4 and page 25, line 10). However, the dissolution rates of the formulation of example 4, Applicant respectfully submits, are different from Applicant's claimed formulations. The actual percentages are different. The Example 4 dissolution described at page 9, is after 2 hours .35% diltiazem is released, after 4 hours 5.10% diltiazem is released. In Applicant's claims between about 1% to about 15% is released after two hours and about 7% to about 35% after four hours. Applicant's more restricted claims claim amounts of about 4% to about 8% after two hours and about 16% to about 21% after four hours. Therefore, the '313 application neither teaches nor contemplates Applicant's claimed formulation. Therefore, it cannot constitute a basis for rejection under

35 U.S.C. §102. The Examiner next asserts Applicant's claims are obvious over '313 stating

> "Further, the formulation also releases the drug at the same rate as that claimed by applicant, therefore, it appears that these limitations do not render any unexpected results. It is the position of the examiner that these are limitations which would be routinely determined by one of ordinary skill through minimal experimentation, as being suitable, absent the presentation of some unusual and/or unexpected results. The results must be based on the specific limitations."

Firstly, Applicant has shown that '313 does not teach Applicant's claims and denies the Examiner's statement "...the formulation also releases the drug at the same rate as that claimed by Applicant." as discussed above.

Additionally, Applicant respectfully submits that there is unexpected results by using Applicant's claimed invention. In this regard, the Examiner is referred to the following:

The '313 Application corresponds in whole and in part to a number of United States patents in the same patent family including United States Patent No. 4,917,899; 4,894,240; 4,891,230; 4,721,619; and 5,002,776 (the family of patents listing is enclosed as **Schedule "A"**). Applicant's reasons for bringing this correspondency to the Examiner's attention will become clear from the following:

Cardizem CD is a formulation containing Diltiazem HCl. Among the patents listed in what is known as "the Orange Book" (Approved Drug Products – The products in this list have been approved under Section 505 of the Federal Food, Drug and Cosmetic Act) are three patents filed by Carderm - United States Patent Nos. 5,286,497; 5,439,689 and 5,470,584 (in addition to a number of the Elan patents including United States Patent No. 4,894,240) – an excerpt from the Orange Book and the cover is attached as **Schedule "B"**.

U.S. Patent 5,286,497 issued from U.S. Application 58,534 which was a continuation of Application 872,572 which is a continuation of Application 702,567. U.S. Patent 5,439,689 issued from Application 164,062 which was a

continuation of Application 58,534 (Patent 5,286,497). U.S. Patent 5,470,584 issued from Application 394,573 which was a continuation of Application 164,062 (Patent 5,439,689).

Application 702,567 filed May 20, 1991

The broadest claim filed in the application is set out as follows:

> 1. A diltiazem bead comprising:
>
> a) a central core containing an effective amount of diltiazem or a pharmaceutically acceptable salt thereof, optionally in association with pharmaceutically acceptable excipients, and;
>
> b) a sufficient quantity of a suitable polymeric coating material which substantially envelops said diltiazem core so that said diltiazem bead exhibits the following in vitro dissolution profile when measured in a type 2 dissolution apparatus (paddle), according to U.S. Pharmacopoeia XXII, at 37°C in 0.1 N HCl at 100rpm:
>
> a) from 0-45% of total diltiazem is released after 6 hours of measurement in said apparatus;
>
> b) from 0-45% of total diltiazem is released after 12 hours of measurement in said apparatus,
>
> c) from 0-75% of total diltiazem is released after 18 hours of measurement in said apparatus, and;
>
> d) not less than 40% is released after 24 hours of measurement.

The Examiner rejected the claims filed under 35 USC §112 as being indefinite for failing to particularly point and distinctly claim the subject matter which applicant regards as the invention. The Examiner also rejected the application in view of Geoghegan in view of Joshi under 35 USC 103 (obviousness) asserting that:

> Geoghegan, teaches a diltiazem pellet comprising a central core (col. 2, lines 27-50), from 0-45% of total diltiazem is released between 6-12 hours (col. 2, lines 53-54) and from 0-75% of diltiazem is released after 18 hours (col. 2, lines 55-56). While Geoghegan does not teach the use of diltiazem ... beadlets. Joshi, teaches a pharmaceutical

composition in the form of beadlets (col. 2, lines 11-14). It would have been obvious to one skilled in the art at the time of the invention to ... combine the teachings of Geoghegan in view of Joshi because Geoghegan, teaches as conventional a novel diltiazem pellet formulation comprising a core of diltiazem surrounded by an multiplicity of sequentially applied and dried layers of a film forming polymer for a controlled absorption rate over a period of time. Joshi, teaches a novel pharmaceutical composition of beadlets which acts as a controlled release formulation.

(Geoghegan is U.S. Patent 4,917,899 and Joshi is U.S. Patent 4,808,413.) – (The Examiner also cited in later actions United States Patent No. 4,894,240.)

An amendment was filed in response to this action wherein Claim 1 was cancelled and Claim 2 was amended as follows:

2. A diltiazem bead comprising:

a) a central core containing an effective amount of diltiazem or a pharmaceutically acceptable salt thereof, optionally in association with pharmaceutically acceptable excipients, and;

b) a sufficient quantity of a suitable polymeric coating material which substantially envelops said diltiazem core so that said diltiazem bead exhibits the following in vitro dissolution profile when measured in a type 2 dissolution apparatus (paddle), according to U.S. Pharmacopoeia XXII, at 37°C in 0.1 N HCl at 100rpm:

[A bead according to claim 1 which exhibits the following in vitro dissolution pattern:

a) from 0-15% of total diltiazem is released after 6 hours of measurement in said apparatus;]

b)] a) from 0-15% of total diltiazem is released after 12 hours in said apparatus;

[c)] b) from 0-45% of total diltiazem is released after 18 hours of measurement in said apparatus, and;

[d] c) not less than 45% of total diltiazem is released after 24 hours of measurement in said apparatus.

In making the proposed amendment the applicant submitted in part as follows:

> Geoghegan et al is directed to diltiazem pellets suitable for incorporation into a product allowing controlled absorption over a twelve hour period. The USPTO has stated that Geoghegan et al renders claim 2 obvious since it discloses pellets having the following dissolution profiles:
>
> b) from 0-15% of total diltiazem is released between 6-12 hours, and from 0-45% of total diltiazem is released by 18 hours (both at Column 2, lines 54-56). This is factually incorrect and the reference does not disclose any pellets having such a dissolution profile.
>
> The Examiner's attention is directed to column 2, lines 53-56 of Geoghegan et al which discloses pellets having the following profiles that:
>
> a) from 0-25% of the total diltiazem is released after 4 hours of measurement in said apparatus;
>
> b) from 20-45% of the total diltiazem is released after 6 hours of measurement in said apparatus, and;
>
> c) not less that 85% of total diltiazem is released after 13 hours of measurement in said apparatus. The USPTO statements regarding claims 10, 11 and 12 are also factually incorrect.
>
> To insure the accuracy of the record the undersigned would like to point out that the dissolution profiles in Geoghegan et al were conducted in 0.05M KCl at pH7.0, whereas those presented in the instant application are carried out in 0.1N HCl.

(The Examiner should examine the entire file history for all submissions.) In the prosecution, the Applicant also submitted as follows:

The present invention is directed to minimizing the variance between peak and trough levels of diltiazem that have been associated with prior art once-a-day diltiazem formulations such as those encompassed by United States Patent 4,894,240. This is accomplished by utilizing a controlled release formulation containing two types of beads having differing but predetermined release rates. One type of bead is a delayed release bead as described by claims 2-10 in which most of the diltiazem is released from the bead 12 hours to 24 hours after immersion into the test medium. Geoghegan et al would not motivate one of ordinary skill in the art to produce a diltiazem bead in which most of the diltiazem is released 12 hours after immersion into the test medium.

By Official Action dated June 26, 1992 (Paper No. 8) the Examiner again rejected the application stating:

Applicant's arguments filed 4/10/92 have been fully considered but they are not deemed to be persuasive.

The applicant argues that the diltiazem pellets for controlled absorption taught by Geoghegan does not disclosure the dissolution profile of the applicants invention. Furthermore, there is no motivation by Geoghegan to produce a diltiazem bead in which most of the diltiazem is released 12 hours. The examiner does not agree with the applicants arguments since it was already disclosed in the previous office action that Geoghegan, teaches a diltiazem pellet which releases from 0 to 25% of total diltiazem after 4 hours, from 20 to 45% after 6 hours and not less than 85% after 13 hours. The profile of Geoghegan reads directly on the claimed invention of the applicant. Joshi, teaches a diltiazem bead in a polymeric coating. One skilled in the art would recognize that the constituent components can be adjusted according to the parameters judged necessary. The examiner does not have to copy every parameter of said claimed invention with the cited references under 35 USC 103 to render said claims obvious. Since Joshi, was not cited for teaching said dissolution profile the applicants argument without merit.

It is the examiners opinion that all of the parameters of the claimed invention have been fully met by the cited references of Geoghegan and Joshi. It would have been prima facie to one skilled in the art that either combined or alone the cited references would motivate one to produce a diltiazem bead with the claimed dissolution profile. The motivation lies in the references of Geoghegan who teaches the use of diltiazem pellets with the claimed dissolution profile.

The Examiner thus concluded that Geoghegan teaches a diltiazem pellet which releases from 0-25% of total diltiazem after 4 hours, from 20-45% after 6 hours, not less than 85% after 13 hours. The profile of Geoghegan, according to the Examiner, reads directly on the claimed invention.

Application 702,567 was abandoned in favour of Application 872,572.

Application 07/872,572

In an Official Action dated 07/20/92 the Examiner relied on Geoghegan '240 (U.S. Patent 4,894,240) together with Stevens stating:

> Geoghegan, teaches a diltiazem bead comprising a central core containing diltiazem (co. 2, lines 21-25), polymeric coating which envelops said diltiazem (col. 2, lines 24-29), with said dissolution profile (col. 2, lines 36-52). While Geoghegan does not teach said specific polymer, Stevens teaches said compositions (col. 1, lines 40-44). It would have been obvious to one skilled in the art at the time of the invention to modify and incorporate the teachings of Geoghegan in view of Stevens because Geoghegan teaches as conventional a novel controlled absorption diltiazem formulations in pellet/bead forms. Stevens teaches a novel sustained release pharmaceutical compositions which comprises diltiazem.
>
> In claims 2, 10, 11, 12, 13, 14, 15 and 16 Geoghegan teaches a bead exhibiting said vitro dissolution pattern (col. 2, lines 42-51; col. 3, lines 3-15).

The claims were not amended in the response but for a minor amendment. Applicant submitted as follows:

> As is discussed in the introduction of the specification, the present invention is directed to a diltiazem formulation which solves the problems associated with prior art once-a-day diltiazem formulations. Diltiazem is subjected to a first-pass effect after administration. This means that a large percentage of the administered dose is metabolized by the liver and rendered inactive before it has had an opportunity to reach the general circulation. Thus, prior art formulations designed to provide zero order release ← of a drug are inappropriate for diltiazem. The release of a constant amount of diltiazem results in the inactivation of a significant

percentage of the administered dose resulting in sub-therapeutic blood levels. It is necessary to use a controlled release formulation with diltiazem. The formulation must release sufficient diltiazem at appropriate times to allow the saturation of the liver's metabolic capacity, so that blood levels of diltiazem can rise significantly to therapeutic levels.

The controlled release formulations of the instant invention provide a release pattern which solves this problem. This formulation is composed of two types of diltiazem beads having differing release rates. One type of diltiazem bead can be characterized as a delayed release diltiazem bead. Minimal diltiazem is released from this bead until 12 hours after immersion into a test medium. The second type of bead is a rapid release bead in which substantially all of the diltiazem is released in the first 8 hours after immersion into the test medium. Claims 2-10 are directed to the delayed release beads and claims 11-16 are directed to formulations containing both types of beads.

The applicant also submitted the following with respect to Geoghegan '240:

Geoghegan #240 is directed to a once-a-day diltiazem formulation. This formulation is designed to produce peak plasma levels of diltiazem 10-14 hours after administration and more preferably from 12-14 hours after administration. This delayed release profile is accomplished by utilizing diltiazem pellets that are coated with a multi-layered polymeric membrane having a specific dissolution profile. These coated diltiazem pellets are combined with up to 25 w/w% of uncoated diltiazem pellets thereby producing the final formulation.

As noted above, the formulation of the instant invention contains two types of diltiazem pellets, both of which contain polymeric coatings. One type can be characterized as a rapid release pellet. It is designed to release up to 100% of its diltiazem within 6 hours after testing. The second type of bead can be characterized as a delayed release bead and it does not release substantial quantities of diltiazem until 12 hours after testing. Claims 2-10 are directed to only the delayed release pellets and claims 11-16 are directed to the final formulation containing both rapid release beads and delayed release beads.

The USPTO has taken the position that claims 2-16 are obvious since Geoghegan teaches polymeric coated diltiazem pellets having dissolution profiles similar to those instantly claimed, and that Stevens teaches the specific polymers utilized in the instant invention. Thus, the instant invention can be produced by modifying the pellets of Geoghegan with the polymers of Stevens.

It is respectfully submitted that this rejection should be removed because Geoghegan #240 does not teach a dissolution profile similar to that contained in claims 2-16. The release rates of Geoghegan's coated pellets differ substantially from those of the instant invention. The release rates of Geoghegan #240 and those of the instant invention are specified below. The release rates are calculated in differing solvent systems (KC1 vs HCl). Despite the differing solvent systems, the release rates are so divergent as to demonstrate the unobviousness of the instant invention.

Geoghegan #240

POLYMERIC COATED DILTIAZEM PELLETS

Time	**% dissolution in Kcl**
2 hours	0-35%
4 hours	5-45%
8 hours	30-75%
13 hours	60-95%

Invention

RAPID RELEASE PELLETS

Time	**% Dissolution**
3 hours	0-40
6 hours	30-100

DELAYED RELEASE PELLETS

Time	**% Dissolution**
12 hours	0-15
18 hours	0-45
24 hours	≥45

Geoghegan discloses a diltiazem pellet which releases from 60-95% of its diltiazem within 13 hours of testing. Claims 2-10 are directed to a diltiazem pellet in which no more than 15% of its diltiazem is released during the first 12 hours of testing. In order to arrive at Applicants invention by modifying Geoghegan's pellets, it would necessary to decrease Geoghegan's release rate by a factor of nearly 400% (ie. ≤15% of diltiazem is released vs. ≥60% in a comparable time frame).

the art of record provides no motivation for decreasing Geoghegan's release rate so dramatically. Such a drastic modification can not be considered merely optimization. **The prior art must provide the motivation to make the modifications necessary to arrive at the claimed invention, In re Lalu 223 USPQ 1257 (1984). The art of record provides no such motivation.**

The subject mater of claims 11-14 is directed to a formulation containing the delayed release pellets in combination with the rapid release pellets. To arrive at the claimed subject matter, it would be

necessary to make two significant modifications to Geoghegan's coated pellets. To produce the rapid release pellets it would be necessary to increase the dissolution profile for some of Geoghegan's polymeric coated pellets (i.e., up to 100% in 6 hours versus ≥60% in 13 hours). It would also be necessary to decrease the dissolution profile of Geoghegan's remaining pellets by a factor of 400% as described above for the delayed release pellets. It would also be necessary to remove all of the uncoated pellets from Geoghegan's formulation. Neither Geoghegan nor Stevens provides the motivation for producing a formulation containing these two types of polymeric coated diltiazem pellets having the dissolution profiles specified above. Again, such a drastic modification cannot be considered to be merely optimization. Finally, Geoghegan #240 teaches away from the dissolution profile encompassed by claim 2-16. The Examiner's attention is directed to Column 2 of the Geoghegan patent, lines 1-15 and lines 53-61, for the specific passages. Geoghegan #240 teaches that in order to produce a once-a-day diltiazem formulation, it is necessary to achieve peak plasma levels of diltiazem 10-14 hours after administration and more preferably 12-14 hours. Further, formulations producing peak plasma levels of diltiazem 6-9 hours after administration are only suitable for twice-a-day administration.

The Examiner's attention is directed to page 34 of Applicants' specification, Table XI, which outlines the pharmacokinetic profile of the formulation of Example #3. This formulation exhibits a release rate corresponding to the subject matter of claims 2-16. This Table is reproduced below for the Examiner's convenience:

TABLE XI

Pharmacokinetic Parameter	Oral Solution	Once a Day Capsule
AUC	910.3 ng/mLxhr	849.1 ng/mLxhr
Cmax	78.6 ng/mL	54.4 ng/mL
Trough	19.8 ng/mL	24.7 ng/mL
Ratio	4.7	2.9
Tmax	1.3 hours	**7.3 hours**
F	1.0	0.93

Examination of this Table shows that the formulation of the instant invention, having the dissolution rates specified above, produced peak plasma levels of diltiazem approximately 7 hours after administration. Geoghegan teaches that such a formulation would not be suitable for once-a-day administration. However, as demonstrated in Table X, this formulation produced therapeutic levels of diltiazem over a 24 hour period. Thus, Geoghegan #240 teaches away from the instant invention rather than suggesting such a formulation.

> The Examiner's attention is also directed to page 3, line 30 through page 4, line 27, of Applicants' specification which discusses Geoghegan #240. Applicants have found that the formulation of Geoghegan produced a wide variance between peak and trough plasma levels of diltiazem. The formulations of the instant invention minimizes this variance. (emphasis added)

The Examiner issued a further action on November 10, 1992, once again rejecting the claims and stating:

> Applicant's arguments filed 08/14/92 have been fully considered but they are not deemed to be persuasive.
>
> The applicants argue that the cited references of Geoghegan #240 and Stevens does not teach a dissolution profile similar to the claimed invention is without basis or merit. The applicant also argues that the release rates are calculated in different solvent systems (KC1 vs HC1). Despite the differing solvent systems, the release rates are so divergent as to demonstrate the unobviousness of the claimed invention. The examiner finds the applicants argument (absent of a declaration providing the different release rates of KC1 vs HC1) without merit as the release rates of diltiazem pellets with respect to the amount of polymeric coatings for said varying pellets are not persuasive because generally it is obvious to the person having ordinary skill in the art to manipulate the proportions of the components to achieve a desired dissolution profile.
>
> Geoghegan teaches a dissolution profile of from 2 to 24 hours not the 13 hours upper limit that the applicant recites from the Geoghegan reference which encompass said vitro dissolution pattern claimed by the applicant. Furthermore, Stevens teaches a sustained release pharmaceutical composition with a controlled dissolution of the active principle over a long period of time and said coating film (the thickness) can be varied. This strongly suggests a coating mixture capable of reading on the dissolution rates as claimed by the applicant and does not read away from the claimed invention. The test for combining references is what the combination of disclosures take as a whole would suggest to one of ordinary skill in the art. In re Simon, 174 USPQ 114 (CCPA 1972); In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). Suggestion of the claimed invention in any or all of the references but what the references taken collectively would suggest.

> It is the examiners opinion that all of the parameters of said claimed invention have been fully met by the combined cited references disclosed. The applicant is reminded that the provisions under 35 USC 103 does not make it mandatory to read on every single parameter of said claims. It would be prima facie obvious to one of ordinary skill in the art to modify and combine the teachings of Geoghegan in view of Stevens. The motivation lies in the controlled and sustained release of Diltiazem with said claimed polymeric coatings with said dissolution profiles. (emphasis added)

Application 08/058,534

Applicant next filed this application as a continuation application together with a preliminary amendment enclosing a number of declarations. The applicant reiterated the grounds for rejection by the Examiner and stated:

> In response thereto, the enclosed declarations provide information concerning the different release rates of KCl vs. HCl. More importantly, they demonstrate that in clinical studies, representing actual use situations, the claimed invention **provides an entirely different release rate from the Elan formulations which are the subject of the Geoghegan '242 patent**. In addition, it is **submitted that the clinical studies demonstrate new and unexpected results for the claimed composition vis-à-vis the two Elan formulations. Such evidence of new and unexpected results is believed sufficient to** rebut any prima facie case of obviousness which may be said to exist (the actual existence which is denied) with the combination of Geoghegan '242 and Stevens.

The applicant, for the first time, with evidence, claimed that its invention provided an entirely different release rate from the Elan formulations which are the subject to the Geoghegan #242 (*sic*) patent. In this regard, the declaration by Diane L. Peterson is enclosed in **Schedule "C"**. The declaration of V.J. Bhargava also enclosed with **Schedule "C"** discussed blood plasma samples and, after reviewing the attached declaration of Dr. Weir (also enclosed in **Schedule "C"**), it was Dr. Bhargava's opinion that the present invention is superior to those described by the '240 patent. The reason for this superiority is based upon the substantially higher trough levels provided by the formulation of the instant invention when compared with that obtained by the Elan formulations. He then continued:

The trough level is the plasma concentration of drug that is achieved by a given formulation immediately prior to the scheduled administration of the next dose. A good sustained release product provides trough plasma concentrations that may be comparable to those obtained when the product may be given in divided doses 3 to 4 times a day. If this quality is lacking the patient may be achieving sub-therapeutic trough levels and may lack efficacy over part of the dosing period.

The trough levels obtained with the two Elan formulations, the 60mg tablets administered 4 times daily and the formulation of the instant invention are presented immediately below for the Examiner's convenience:

MEAN TROUGH LEVELS

TREATMENT	TROUGH LEVEL ng/ml
Elan A	48.5
Elan B	46.0
60 mg qid	67.3
Invention	**66.5**

levels produced by the two Elan formulations are approximately 30% below that produced by the formulation of the instant invention. The significantly lower level of drug may correspond to a decreased therapeutic effect over the relevant portion of the dosing period.

Another advantage of the formulation of the instant invention is how closely the trough levels correspond to those obtained with the 60mg tablets administered 4 times daily. This will facilitate the conversion of the patient from a dosage form requiring administration 4 times daily to the convenience of a once a day dosage form.

The final declaration was that of Scott Weir, also enclosed with **Schedule "C"**, describing how the '240 diltiazem formulations made by the Elan patent were obtained from Elan Corporation plc which identified the formulation and which gave the release profiles:

The dissolution profiles of each of these formulations was evaluated in 0.05M KCL as described in the '240 patent beginning at line 65, column 2. This dissolution testing was carried out at Elan's facilities by Elan personnel and the results were provided to MMD.

Elan formulation A exhibited the following dissolution profile:

DISSOLUTION PROFILE

TIME	% DILTIAZEM HCl RELEASED
2 Hr	12.2
4 Hr	18.1
6 Hr	34.2
8 Hr	50.8
10 Hr	64.4
13 Hr	79.7
24 Hr	97.6

Elan formulation B exhibited the following dissolution profile:

DISSOLUTION PROFILE

TIME	% DILTIAZEM HCl RELEASED
2 Hr	14.7
4 Hr	21.5
6 Hr	36.9
8 Hr	53.8
10 Hr	69.0
13 Hr	82.5
24 Hr	102.2

Pharmacokinetic profiles of the two Elan formulations were determined in a study and blood plasma samples were drawn from the volunteers identified at page 4. The diltiazem mean plasma concentrations for the two formulations are set out at pages 5 and 6 as follows:

TABLE I ELAN FORMULATION A

Time 6th Dose:	Diltiazem Mean Plasma Concentration (ng/ml) (% CV)	
0 hours	49.31	(31.28%)
7th dose		
0 hours	48.62	(31.02%)
2 hours	75.04	(36.64%)
4 hours	65.89	(37.53%)
6 hours	63.92	(36.31%)

7 hours	71.32	(37.11%)
10 hours	98.14	(27.59%)
12 hours	104.24	(25.86%)
14 hours	95.92	(26.10%)
16 hours	84.99	(23.44%)
18 hours	75.94	(25.34%)
20 hours	61.89	(23.78%)
22 hours	53.34	(25.37%)
24 hours	47.70	(25.85%)
30 hours	28.50	(30.07%)

TABLE II ELAN FORMULATION B

Time 6th Dose:	Diltiazem Mean Plasma Concentration (ng/ml)	(% CV)
0 hours	47.73	(36.84%)
7th dose		
0 hours	47.15	(33.84%)
2 hours	94.52	(27.55%)
4 hours	77.13	(31.83%)
6 hours	69.78	(33.79%)
7 hours	70.15	(31.41%)
10 hours	91.36	(29.85%)
12 hours	94.97	(29.27%)
14 hours	84.36	(25.43%)
16 hours	78.47	(27.43%)
18 hours	69.00	(25.20%)
20 hours	56.63	(26.07%)
22 hours	48.57	(25.20%)
24 hours	43.05	(24.63%)
30 hours	27.75	(37.10%)

TABLE III Cardizem Tablets

Time 21st Dose:	Diltiazem MeanPlasma Concentration (ng/ml)	(% CV)
0 hour	71.31	(28.42%)
25th dose		

0 hour	66.47	(30.79%)
1 hour	86.19	(29.73%)
2 hours	107.98	(27.01%)
3 hours	127.01	(24.28%)
4 hours	108.94	(26.40%)
6 hours	73.11	(25.60%)
26th dose		
1 hour	82.15	(25.82%)
2 hours	105.69	(28.46%)
3 hours	110.13	(23.39%)
4 hours	94.10	(21.72%)
6 hours	61.90	(26.95%)
27th dose		
1 hour	58.29	(30.48%)
2 hours	79.66	(28.42%)
3 hours	93.11	(26.33%)
4 hours	77.48	(25.04%)
6 hours	55.05	(24.25%)
28th dose		
1 hour	60.26	(37.97%)
2 hours	64.96	(36.89%)
3 hours	70.69	(31.47%)
4 hours	73.61	(26.37%)
6 hours	64.19	(25.97%)
12 hours	24.94	(33.39%)

With further information given and Table III with respect to the Cardizem tablets after the 21st dose, 25th dose, 26th dose, 27th dose and 28th dose. At page 6, Table IV provides trough- average of 7 a.m. plasma concentrations obtained prior to dosing on day 6 and 7 in addition to 24 hours post-dose and H8 are given together with other data.

The Mean values for the following pharmacokinetic parameters were determined from the plasma diltiazem concentration time profiles: AUC-Area under the curve, Cmax - Maximum steady-state plasma concentration, Trough - average of 7 AM plasma concentrations obtained prior to dosing on days 6 and 7 in addition to 24 hours post-dose on day 8, Ratio- ratio of C-max to C-min, the minimum steady state plasma concentration, Tmax - time to maximum concentration. These mean values are reported below in Table IV (Value in parenthesis represents % CV).

TABLE IV

	Tablet 60 mg qid	Elan A 240 mg/ day	Elan B 240 mg/day
AUC (0-24 hr) (ng/mixhr)	1960 (23)	1801 (26)	1760 (26)
CMAX (ng/ml)	129 (23)	108 (26)	106 (27)
RATIO (CMAX/CMIN)	2.8 (17)	2.5 (20)	2.6 (15)
TMAX (hr)	4.0 (57)	11.8 (22)	8.1 (62)
TROUGH (ng/ml)	67.3 (26)	48.5 (27)	46.0 (29)

The applicant in a further response enclosing revised claims thanked Examiner Page for the interview and made the following submissions (also made at the interview):

> During that interview, it was explained that the assignee of the present invention, Carderm, is a recent spin-off of Marion Merrell Dow Inc., which has for years sold diltiazem HCl under the trademark Cardizem. The once-a-day form of Cardizem, then, is sold under the trademark Cardizem CD. Enclosed is a copy of the advertising literature concerning Cardizem CD, which literature was shown to Examiner Page during the interview. The once-a-day diltiazem formulation sold under the trademark Cardizem CD is the subject matter of the present application. Examiner Page was also shown one of the Cardizem CD capsules and it was explained that that capsule contained a blend of A) rapid release diltiazem beads and B) delayed release diltiazem beads. Dr. Bhargava explained that because diltiazem has a relatively short half life and because it absorbs throughout the gastrointestinal track, it has been found that a "stair-step release profile" for the once-a-day formulation is highly desirable.
>
> That is, when compared to Geoghegan Patent No. 4,894,240, which is the principal reference relied upon by the Examiner in this case, there is a considerable difference in the drug release mechanism involved. In the Geoghegan patent, the coated drug has a coating which is a mixture of a water insoluble and water soluble material. Upon dissolution of the water soluble material, the coating on the drug becomes porous and the drug is gradually released steadily over a period of time. In the Geoghegan formulation, some free

drug (uncoated) is also blended with that coated drug in order to obtain some immediate release of the drug. The net result is a release curve which rises rapidly and then gradually tapers off.

On the other hand, as Dr. Bhargava explained, the release profile for Cardizem CD is a "stair-step" one. That is demonstrated by the Bhargava and Weir declarations, which were previously submitted in this case and by the Peterson declaration which was shown to Examiner Page and which is enclosed herewith. Note, as shown in the Peterson declaration, that at 13 hours the blended formulation of the present invention has a release of 33.9%; whereas, in Geoghegan Patent No. 4,894,240, the release after 13 hours is 60-95%. That is, the blended diltiazem formulation of the present invention has a "flat step" of the "stair-step release profile" at around 13 hours. Such a release profile is not shown in the art of record, as recognized by Examiner Page. That is, in the Examiner Interview Summary Record, it is stated: "Claim 11 represents the invention of a mixture of distinctly coated beads in a formulation having a specific dissolution profile. Claims presented define over the prior art of record."

... patentable subject matter in the combination of previous claim 11 (which covers the blend of rapid release coated diltiazem beads and delayed release coated diltiazem beads as specified) and the specific dissolution profile of the blend (which was previously the subject matter of dependent claim 15), new independent claim 17 is presented herewith. Claim 17 is essentially a combination of previously pending claims 2, 11, and 15. As Examiner Page requested, it sets forth the blend of rapid release coated diltiazem beads having a specific profile, and delayed release coated diltiazem beads having a specific profile; with the blend, then, having the specific release profile set forth. Claims 18-29 depend from independent claim 17. All other claims have been canceled.

The case was allowed. The claims issued in U.S. Patent 5,286,497 (which the Examiner can review).

Application 08/164,062

This application was filed as a continuation and subsequently issued as U.S. Patent 5,439,689.

The Examiner allowed the claims. The Examiner stated in his reasons for allowing the case:

> The following is an Examiner's Statement of Reasons for Allowance: The optimized blood levels of diltiazem over a 24 hour period is accomplished by a controlled release dosage form which exhibits a release profile wherein decreasing the variance between peak and trough levels of diltiazem is not taught or suggested by the prior art of record.

Therefore the optimized blood levels for the diltiazem from the formulation provides a decrease in the variance between peak and trough levels of diltiazem of the prior art which was not taught or suggested by the prior art of record.

Application 394,573

A preliminary amendment was filed by which the pending claims were cancelled and new claims were inserted. These claims, however, only claimed a delayed release diltiazem formulation.

The Examiner rejected these claims based on the obviousness type double patenting having regard to U.S. Patent 5,286,497 and required a terminal disclaimer. A terminal disclaimer was filed and the patent issued.

Further with respect to the formulations claimed in the claims of U.S. Patent 5,470,584 although relating to a delayed release formulation, the claimed subject matter was nevertheless found to be the same invention as U.S. Patent 5,286,497 and therefore a terminal disclaimer had to be made. The release from the delayed release components for both was the same and provided a maximum release at 18 hours of 75%. All of the claimed formulations of the three patents gave, according to the Examiner, a decrease in the variance between the peak and troughs of the blood plasma levels.

Applicant encloses data in **Schedule "D"** which, in Applicant's respectful submission, substantiate that its claimed formulation provides unexpected results over '313. Table 1 compares Cardizem CD, which was found by Examiner

Page to exhibit a release profile wherein decreasing the variance between peak and trough levels of diltiazem was not taught or suggested by the prior art of record with Applicant's formulation. In Table 1, Cardizem CD exhibited 106.85% variance. Applicant's claimed invention (Diltiazem HCl ER capsules) exhibited 84.98% variance. Therefore, Applicant's claimed invention exhibits at least the same decreasing variance as Carderm CD and therefore exhibits "unexpected results" which the Examiner stated was lacking. Thus, in Applicant's respectful submission, Applicant's claimed invention is meritorious, inventive and allowable. There is no motivation in '313 to make Applicant's claimed formulations. '313 does not teach Applicant's benefits.

Applicant also encloses in further support, as **Schedule "E"**, an article by Eradiri, O. et al., entitled "Comparison of diltiazem bioavailability from 3 marketed extended-release products for once-daily administration: implications of chronopharmacokinetics and dynamics", International Journal of Clinical Pharmacology and Therapeutics, (1997), Vol. 35, No. 9, p. 369-373. This article shows at page 372 the degree of fluctuation of Cardizem CD (134±40%) and Tiazac (139±36%) – Tiazac will be discussed with respect to Deboeck ('093).

The '093 Patent Application

The Examiner has also rejected the claimed invention in view of '093 under 35 U.S.C. §103(a). In doing so, the Examiner admits that '093, "does not teach the exact rates of release as claimed by Applicant, nor do they discuss the rates of release after 8 hours, nor do they disclose all the specific amounts of the above-mentioned ingredients." The Examiner however takes the position that '093 does teach overlapping release rates and while '093 does not teach a Cmax at 10-15 hours (Tmax) as claimed by Application, the claims are obvious. The broad release rates of '093 at page 4, lines 24-34 are not those in Applicant's claims. The examples at page 5, lines 16-20, page 14, lines 16-21 and page 15, lines 9-13 (Example 4) are not within Applicant's claimed ranges. Nor is the Cmax of '093 between about 10-15 hours (Tmax). Figure 1 shows a Tmax at 8-9 hours. Figure 1 shows a steady state plasma level after 7 days administration of the Example 4

dosage (see page 15, lines 15-31). Figure 2 appears to have a Cmax at Tmax of 10-11 hours. However, Example 4 does not have a release profile within Applicant's claimed release profiles. Despite these differences, the Examiner still maintains obviousness stating "Applicant's invention is not patentably distinct from the prior art.

Applicant respectfully further responds to this ground of rejection as follows:

WO 93/00093 (Deboeck) corresponds to United States Patent No. 5,529,791 and United States Patent No. 5,288,505 (see the Family of Patent listing enclosed as **Schedule "F"**). United States Patent No. 5,529,791 is identified as relating to Tiazac in the Orange Book extract enclosed as **Schedule "B"** herein. As discussed in **Schedule "E"**, Tiazac has a fluctuation of (139±36%), a greater fluctuation (even at its best reading) than with respect to **Schedule "D"** (which compares a formulation using Applicant's claimed invention and Cardizem CD). The Examiner's attention is also directed to Figure 8 of the application which graphically illustrates the differences in Tiazac and formulations in accordance with this application. There is, once again, no motivation to make Applicant's claimed formulation in '093. '093 does not teach Applicant's benefits.

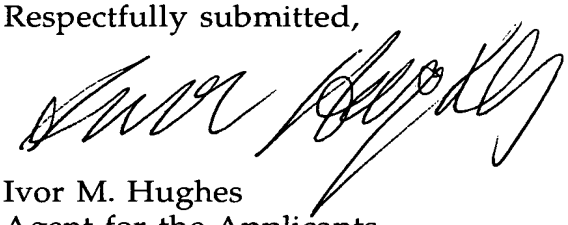
In view of the above submissions, Applicant submits that all claims herein are inventive over the prior art provide unexpected utility over all prior art and Applicant respectfully requests allowance of same.

Applicant has enclosed one cheque in the sum of $1,600.00 U.S. which incorporates the fee of $890.00 U.S. for the three month extension of time and $710.00 U.S. for the base filing fee for a Request for Continued Examination (RCE). If there should occur an overpayment or an underpayment of fees in respect of this submission, the Commissioner is authorized to access Deposit Account Number 08-3255 to make the appropriate adjustments and advise Applicant's agent.

If the Examiner has any questions, she is respectfully requested to contact Applicant's agent, Ivor M. Hughes, at area code 905-771-6414, collect at the Examiner's convenience.

Once the Examiner has received and examined the Request for Continued Examination (RCE) and Submission, Applicant's agent requests that the Examiner call Applicant's agent collect at her convenience to arrange for an interview at a time suitable to the Examiner.

Respectfully submitted,



Ivor M. Hughes
Agent for the Applicants
Registration No. 27,759

IMH*kdk

Enclosures

1. Request for Continued Examination (RCE) Transmittal
2. Request for Three Month Extension of Time
3. Check in the sum of $1,600.00 U.S.
4. Exhibit A
5. Exhibit B
6. Schedule "A" (family of patents listing)
7. Schedule "B" (excerpt from the Orange Book and the cover)
8. Schedule "C" (declarations by Diane L. Peterson, V.J. Bhargava and Scott Weir)
9. Schedule "D" (data)
10. Schedule "E" (an article by Eradiri, O. et al., entitled "Comparison of diltiazem bioavailability from 3 marketed extended-release products for once-daily administration: implications of chronopharmacokinetics and dynamics", International Journal of Clinical Pharmacology and Therapeutics, (1997), Vol. 35, No. 9, p. 369-373)
11. Schedule "F" (Family of Patent listing)

EXHIBIT A
CLAIMS WITH MARKINGS TO SHOW CHANGES

3. (Amended) The preparation of claim 1 [or 2] wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

9. (Twice Amended) The preparation of claim [1 or] 2 wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane.

12. (Twice Amended) The preparation of claim 9[, 10 or 11] wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer which hydrates the preparation.

14. (Twice Amended) The preparation of claim 9[, 10, 11, 12 or 13] wherein the membrane comprises a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.

17. (Amended) The preparation of claim 1[, 2, 3, 4, 5, 6, 7 or 8] wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

18. (Twice Amended) The preparation of claim 2 [17] wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable

dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation and wherein the dissolution agent is an organic acid selected from the group consisting of adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, and tartaric acid, which permits the diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into higher pH regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

37. (Amended) The preparation of claim [1, 2,] 3[, 4, 7, 8, 9, 11, 12, 13 or 14] wherein the preparation contains 120 mg of Diltiazem.

38. (Amended) The preparation of claim [1, 2,] 3[, 4, 7, 8, 9, 11, 12, 13 or 14] wherein the preparation contains 180 mg of Diltiazem.

39. (Amended) The preparation of claim [1, 2,] 3[, 4, 7, 8, 9, 11, 12, 13, or 14] wherein the preparation contains 240 mg of Diltiazem.

40. (Amended) The preparation of claim [1, 2,] 3[, 4, 7, 8, 9, 11, 12, 13, or 14] wherein the preparation contains 300 mg of Diltiazem.

41. (Amended) The preparation of claim [1, 2,] 3[, 4, 7, 8, 9, 11, 12, 13, or 14] wherein the preparation contains 360 mg of Diltiazem.

42. (Amended) The preparation of claim [1, 2,] 3[, 4, 7, 8, 9, 11, 12, 13, or 14] wherein the preparation contains 420 mg of Diltiazem.

44. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane and [The preparation of claim 9, 10, 11, 12, 13, 14, 15 or 16] wherein the wetting agent is selected from the group consisting of:

sugars;
saccharose, mannitol, sorbitol;
lecithins;
C_{12} to C_{20} fatty acid esters of saccarose,;
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene;
sorbitan fatty acid esters;
polyglycides-glycerides and polyglycides-alcohols esters and
Metal salts.

47. (Amended) A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 3 [45]

to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane and wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

48. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;

(c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane [The preparation of claim 9, 10, 11, 12, 13, 14, 15, 16, 44 or 45] in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

49. (Amended) A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 48 [46] to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

50. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours

(Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane [The preparation of claim 9, 10, 11, 12, 13, 14, 15, 16, 44 or 45] in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

52. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;

(c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane [The preparation of claim 9, 10, 11, 12, 13, 14, 15, 16, 44 or 45] in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

60. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-

release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants [The preparation of claim 56, 57 or 58] wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)8 - 9.5	
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0

(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

62. (Amended) A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 56[, 57, 58, 59, 60 and 61] to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Schedule "A"

(Family of Patents Listing)

ENTER DISPLAY FORMAT (BIB.M):fam

L3 ANSWER 1 OF 1 INPADOC COPYRIGHT 2001 EPO

PATENT FAMILY INFORMATION
AN 26000051 INPADOC

PRAI			AI		
EP 1984-309032	A	19841221	AT 1984-309032	EP	19841221
EP 1988-309665	A3	19881014	EP 1998-105888	A	19881014
IE 1983-3057	A	19831222	AT 1984-309032	EP	19841221
			BE 1984-214218	A	19841221
			CH 1984-6030	A	19841218
			DE 1984-309032	EP	19841221
			EP 1984-309032	A	19841221
			IE 1983-3057	A	19841214
			JP 1984-270584	A	19841221
			PH 1984-31626	A	19841221
			US 1984-684661	A	19841220
			US 1987-120952	A	19871116
			US 1992-921459	A	19920728
			US 1994-334864	A	19941104
IE 1987-2789	A	19871016	IE 1987-2789	A	19871016
			US 1987-121224	A	19871116
IE 1987-2790	A	19871016	AU 1988-23775	A	19881014
			AU 1991-79435	A	19910628
			DK 1988-5756	A	19881014
			EP 1988-309665	A	19881014
			EP 1998-105888	A	19881014
			JP 1988-259304	A	19881014
			KR 1988-13539	A	19881017
			NZ 1988-226575	A	19881014
			PT 1988-88776	A	19881014
			US 1992-918925	A	19920722
			US 1993-64401	A	19930519
			ZA 1988-7681	A	19881014
IE 1987-2791	A	19871016	AU 1988-23775	A	19881014
			AU 1991-79435	A	19910628
			DK 1988-5756	A	19881014
			EP 1988-309665	A	19881014
			EP 1998-105888	A	19881014
			JP 1988-259304	A	19881014
			KR 1988-13539	A	19881017
			NZ 1988-226575	A	19881014
			PT 1988-88776	A	19881014
IE 1987-3158	A	19871120	AU 1988-23775	A	19881014
			AU 1991-79435	A	19910628
			DK 1988-5756	A	19881014
			EP 1988-309665	A	19881014
			EP 1998-105888	A	19881014
			JP 1988-259304	A	19881014
			KR 1988-13539	A	19881017
			NZ 1988-226575	A	19881014
			PT 1988-88776	A	19881014
			US 1988-273192	A	19881118
IE 1988-822	A	19880318	AU 1988-23775	A	19881014
			AU 1991-79435	A	19910628

			DK	1988-5756	A 19881014
			EP	1988-309665	A 19881014
			EP	1998-105888	A 19881014
			JP	1988-259304	A 19881014
			KR	1988-13539	A 19881017
			NZ	1988-226575	A 19881014
			PT	1988-88776	A 19881014
			US	1988-273192	A 19881118
US	1984-684661	A2 19841220	US	1987-120952	A 19871116
			US	1987-121224	A 19871116
			US	1987-121225	A 19871116
			US	1988-273192	A 19881118
			US	1994-334864	A 19941104
US	1987-120952	A1 19871116	US	1992-918925	A 19920722
US	1987-120952	A2 19871116	US	1988-273192	A 19881118
US	1987-121225	A 19871116	US	1987-121225	A 19871116
US	1987-121225	A1 19871116	US	1992-921459	A 19920728
			US	1994-334864	A 19941104
US	1987-121225	A2 19871116	US	1988-273192	A 19881118
US	1989-446116	B1 19891205	US	1992-918925	A 19920722
US	1989-455544	B1 19891229	US	1992-921459	A 19920728
			US	1994-334864	A 19941104
US	1992-918925	A1 19920722	US	1993-64401	A 19930519
US	1992-921459	A 19920728	US	1992-921459	A 19920728
US	1992-921459	A3 19920728	US	1994-334864	A 19941104
US	1993-64401	A 19930519	US	1993-64401	A 19930519
US	1994-334864	A 19941104	US	1994-334864	A 19941104

+----------AI----------+			+----------PI----------+		
AT	1984-309032	EP 19841221	AT	66813	E 19910915
AU	1988-23775	A 19881014	AU	615221	B2 19910926
			AU	8823775	A1 19890608
AU	1991-79435	A 19910628	AU	634660	B2 19930225
			AU	9179435	A1 19910912
BE	1984-214218	A 19841221	BE	901359	A1 19850416
CH	1984-6030	A 19841218	CH	662507	A 19871015
DE	1984-309032	EP 19841221	DE	3485023	C0 19911010
DK	1988-5756	A 19881014	DK	8805756	A 19890417
			DK	8805756	A0 19881014
EP	1984-309032	A 19841221	EP	149920	A2 19850731
			EP	149920	A3 19850828
			EP	149920	B1 19910904
EP	1988-309665	A 19881014	EP	320097	A1 19890614
EP	**1998-105888**	**A 19881014**	**EP**	**856313**	**A1 19980805**
IE	1983-3057	A 19841214	IE	56999	B 19920311
IE	1987-2789	A 19871016	IE	60929	B 19940907
JP	1984-270584	A 19841221	JP	06043312B	B4 19940608
			JP	60156617	A2 19850816
JP	1988-259304	A 19881014	JP	01132521	A2 19890525
			JP	07116044B	B4 19951213
KR	1988-13539	A 19881017	KR	9701656	B1 19970213
NZ	1988-226575	A 19881014	NZ	226575	A 19910129
PH	1984-31626	A 19841221	PH	22003	A 19880502
PT	1988-88776	A 19881014	PT	88776	B 19921231
US	1984-684661	A 19841220	US	4721619	A 19880126
US	1987-120952	A 19871116	US	4891230	A 19900102

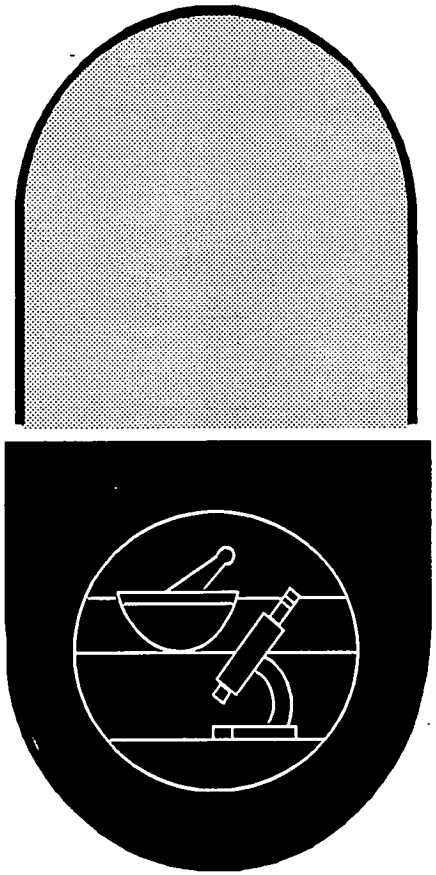
US 1987-121224	**A**	**19871116**	**US 4917899**	**A**	**19900417**
US 1987-121225	A	19871116	US 4894240	A	19900116
US 1988-273192	A	19881118	US 5002776	A	19910326
US 1992-918925	A	19920722	US 5219621	A	19930615
US 1992-921459	A	19920728	US 5364620	A	19941115
US 1993-64401	A	19930519	US 5336504	A	19940809
US 1994-334864	A	19941104	US 5616345	A	19970401
ZA 1988-7681	A	19881014	ZA 8807681	A	19890726

21 priorities, 28 applications, 35 publications

Schedule "B"

(Excerpt from the Orange Book and the cover page)

MAY - 1 2000



APPROVED DRUG PRODUCTS

WITH THERAPEUTIC EQUIVALENCE EVALUATIONS

20TH EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFORMATION TECHNOLOGY
DIVISION OF DATA MANAGEMENT AND SERVICES

2000

PRESCRIPTION AND OTC DRUG PRODUCT
PATENT AND EXCLUSIVITY DATA

APPL/PROD NUMBER	INGREDIENT NAME; TRADE NAME	PATENT NUMBER	PATENT EXPIRES	USE CODE	EXCLUS CODE	EXCLUS EXPIRES
020405 002	DIGOXIN;LANOXIN				I-194	SEP 30, 2000
020405 003	DIGOXIN;LANOXIN				I-194	SEP 30, 2000
020405 004	DIGOXIN;LANOXIN				I-194	SEP 30, 2000
020405 005	DIGOXIN;LANOXIN				I-194	SEP 30, 2000
020405 006	DIGOXIN;LANOXIN				I-194	SEP 30, 2000
018885 001	DIHYDROERGOTAMINE MESYLATE;EMBOLEX	4451458	MAY 29, 2001			
		4402949	SEP 06, 2000			
018885 002	DIHYDROERGOTAMINE MESYLATE;EMBOLEX	4451458	MAY 29, 2001			
		4402949	SEP 06, 2000			
020148 001	DIHYDROERGOTAMINE MESYLATE;MIGRANAL	4758423	JUL 31, 2001		NDF	DEC 08, 2000
		4462983	JUL 31, 2001	U-227		
020062 001	DILTIAZEM HYDROCHLORIDE;CARDIZEM CD	5169849	DEC 08, 2009	U-227		
		5286497	MAY 20, 2011			
		4894240	JAN 16, 2007			
		5470584	MAY 20, 2011			
		5364620	NOV 14, 2011	U-3		
		5439689	AUG 08, 2012	U-107		
020062 002	DILTIAZEM HYDROCHLORIDE;CARDIZEM CD	5002776	MAR 26, 2008			
		5286497	MAY 20, 2011			
		5364620	NOV 14, 2011	U-3		
		5470584	MAY 20, 2011			
		5002776	MAR 26, 2008			
		4894240	JAN 16, 2007			
		5439689	AUG 08, 2012	U-107		
020062 003	DILTIAZEM HYDROCHLORIDE;CARDIZEM CD	5286497	MAY 20, 2011			
		5439689	AUG 08, 2012	U-107		
		4894240	JAN 16, 2007			
		5002776	MAR 26, 2008			
		5364620	NOV 14, 2011	U-3		
		5470584	MAY 20, 2011			
020062 004	DILTIAZEM HYDROCHLORIDE;CARDIZEM CD	5286497	MAY 20, 2011			
		4894240	JAN 16, 2007			
		5002776	MAR 26, 2008			
		5364620	NOV 14, 2011	U-3		
		5439689	AUG 08, 2012	U-107		
		5470584	MAY 20, 2011			
019471 001	DILTIAZEM HYDROCHLORIDE;CARDIZEM SR	4721619	JAN 26, 2005			
019471 002	DILTIAZEM HYDROCHLORIDE;CARDIZEM SR	4721619	JAN 26, 2005			
019471 003	DILTIAZEM HYDROCHLORIDE;CARDIZEM SR	4721619	JAN 26, 2005			
019471 004	DILTIAZEM HYDROCHLORIDE;CARDIZEM SR	4721619	JAN 26, 2005			
020092 001	DILTIAZEM HYDROCHLORIDE;DILACOR XR	4839177	DEC 09, 2006			
		5422123	JUN 06, 2012			
020092 002	DILTIAZEM HYDROCHLORIDE;DILACOR XR	4839177	DEC 09, 2006			
		5422123	JUN 06, 2012			
020092 003	DILTIAZEM HYDROCHLORIDE;DILACOR XR	4839177	DEC 09, 2006			
		5422123	JUN 06, 2012			
020401 001	DILTIAZEM HYDROCHLORIDE;TIAZAC	5529791	JUN 25, 2013		I-133	JAN 30, 2001

PRESCRIPTION AND OTC DRUG PRODUCT
PATENT AND EXCLUSIVITY DATA

APPL/PROD NUMBER	INGREDIENT NAME; TRADE NAME	PATENT NUMBER	PATENT EXPIRES	USE CODE	EXCLUS CODE	EXCLUS EXPIRES
020401 002	DILTIAZEM HYDROCHLORIDE;TIAZAC	5529791	JUN 25, 2013		I-133	JAN 30, 2001
020401 003	DILTIAZEM HYDROCHLORIDE;TIAZAC	5529791	JUN 25, 2013		I-133	JAN 30, 2001
020401 004	DILTIAZEM HYDROCHLORIDE;TIAZAC	5529791	JUN 25, 2013		I-133	JAN 30, 2001
020401 005	DILTIAZEM HYDROCHLORIDE;TIAZAC	5529791	JUN 25, 2013		I-133	JAN 30, 2001
020507 001	DILTIAZEM MALATE;TECZEM	4472380	SEP 18, 2001			
		4968507	JUL 25, 2006			
		4374829	FEB 22, 2000	U-3		
		4880631	SEP 24, 2007			
		4983598	JAN 08, 2008			
020506 001	DILTIAZEM MALATE;TIAMATE	4880631	SEP 24, 2007			
		4968507	JUL 25, 2006			
020506 002	DILTIAZEM MALATE;TIAMATE	4880631	SEP 24, 2007			
		4968507	JUL 25, 2006			
020506 003	DILTIAZEM MALATE;TIAMATE	4880631	SEP 24, 2007			
		4968507	JUL 25, 2006			
020411 001	DINOPROSTONE;CERVIDIL	4931288	JAN 16, 2007			
		5269321	DEC 14, 2010	U-110		
019617 001	DINOPROSTONE;PREPIDIL	4680312	JUL 14, 2004			
018723 001	DIVALPROEX SODIUM;DEPAKOTE	5212326	JAN 29, 2008			
		4988731	JAN 29, 2008			
018723 002	DIVALPROEX SODIUM;DEPAKOTE	5212326	JAN 29, 2008			
		4988731	JAN 29, 2008			
018723 003	DIVALPROEX SODIUM;DEPAKOTE	5212326	JAN 29, 2008			
		4988731	JAN 29, 2008			
019680 001	DIVALPROEX SODIUM;DEPAKOTE	5212326	JAN 29, 2008			
		4988731	JAN 29, 2008			
019794 001	DIVALPROEX SODIUM;DEPAKOTE CP	4988731	JAN 29, 2008			
		5212326	JAN 29, 2008			
019794 002	DIVALPROEX SODIUM;DEPAKOTE CP	4988731	JAN 29, 2008			
		5212326	JAN 29, 2008			
020449 001	DOCETAXEL;TAXOTERE	4814470	MAY 14, 2010		I-282	DEC 23, 2002
		5438072	NOV 22, 2013		NCE	MAY 14, 2001
		5698582	JUL 03, 2012		I-231	JUN 22, 2001
		5714512	JUL 03, 2012			
020931 001	DOFETILIDE;TIKOSYN				NCE	OCT 01, 2004
020931 002	DOFETILIDE;TIKOSYN				NCE	OCT 01, 2004
020931 003	DOFETILIDE;TIKOSYN				NCE	OCT 01, 2004
020623 001	DOLASETRON MESYLATE MONOHYDRATE;ANZEMET				NCE	SEP 11, 2002
020623 002	DOLASETRON MESYLATE MONOHYDRATE;ANZEMET				NCE	SEP 11, 2002
020624 001	DOLASETRON MESYLATE MONOHYDRATE;ANZEMET				NCE	SEP 11, 2002
020624 002	DOLASETRON MESYLATE MONOHYDRATE;ANZEMET				NCE	SEP 11, 2002
020690 001	DONEPEZIL HYDROCHLORIDE;ARICEPT	4895841	NOV 25, 2010		NCE	NOV 25, 2001
020690 002	DONEPEZIL HYDROCHLORIDE;ARICEPT	4895841	NOV 25, 2010		NCE	NOV 25, 2001
020869 001	DORZOLAMIDE HYDROCHLORIDE;COSOPT	4797413	APR 28, 2008		NC	APR 07, 2001
		4619939	OCT 28, 2003			
020408 001	DORZOLAMIDE HYDROCHLORIDE;TRUSOPT	4797413	APR 28, 2008	U-103		
		4619939	OCT 28, 2003	U-104		

Schedule "C"

(Declarations by Diane L. Peterson, V.J. Bhargava and Scott Weir)

I, Diane L. Peterson, Ph.D., do hereby declare that:

I obtained a Bachelor's of Science in Chemistry from the University of Wisconsin-Eau Claire in 1981. I also obtained a Ph.D. from Purdue University in Analytical Chemistry in August of 1987. From 1987 until the present I have been employed by Marion Merrell Dow, Inc. and its predecessor Marion Laboratories.

I am currently a Group Leader/Scientist in the Analytical Chemistry Department at Marion Merrell Dow, Inc. and have a group of 7 chemists and technicians reporting to me. I am responsible for developing and validating analytical methods for evaluating pharmaceutical dosage forms and providing analytical support for the development of new formulations.

The following dissolution tests were carried out under my direct supervision. The purpose of these tests was to determine the dissolution profile that diltiazem dosage forms encompassed by United States Patent Application Serial No. 08/058,534 would exhibit when tested by the dissolution test described by United States Patent No. 4,894,240.

The dissolution testing was carried out utilizing diltiazem dosage forms prepared in the same manner as disclosed in Example II of United States Patent application 08/058,534. Dissolution testing was carried out on the final dosage form and on the individual bead types (i.e., the rapid release and the delayed release beads).

The dissolution testing was carried out in the manner described by United States Patent No. 4,894,240. Specifically, the method of U.S. Pharmacopeia XXI was used Beads were weighed and handfilled into a 300 mg capsule. Each capsule was tested in 900 mL of 0.05 M KCl, with a type II paddle assembly at a rotational speed of 100 rpm and at a temperature of 37°C. Aliquots were subsequently withdrawn 2, 4, 8, 13 and 24 hours after initiation of the testing. The amount of diltiazem that had been released was measured by UV spectrophotometry with a Hewlett-Packard diode array system. Six capsules were tested for each lot, and the results were averaged. The same testing protocol was used for the final dosage form, the rapid release beads, and the delayed release beads.

The following results were obtained:

TIME (hours)	BLENDED FORMULATION	RAPID RELEASE BEAD	DELAYED RELEASE BEAD
2	1.3	1.2	1.3
4	11.5	30.3	1.3
8	31.7	92.9	1.6
13	33.9	95.9	3.0
24	89.7	97.8	86.1

For comparative purposes, the testing described above was compared to the results obtained for these lots utilizing the protocol described in the instant application, namely by the method of U.S. Pharmacopia XXII in 900 mL of 0.1 N HCl, using a type II paddle assembly at 100 rpm, and at a temperature of 37°C. Samples were prepared in the same manner as described above. Aliquots were withdrawn 3, 6, 9, 12, 15, 18, 21, 24 and 30 hours after initiation of the testing. Multiple capsules were tested for each lot, and the results were averaged. The following results were obtained:

TIME (hours)	BLENDED FORMULATION	RAPID RELEASE BEAD	DELAYED RELEASE BEAD
3	1.0	2.7	0.8
6	18.3	79.0	1.0
9	21.5	93.9	1.0
12	22.3	96.3	1.3
15	23.9	98.0	2.5
18	33.2	98.9	16.2
21	56.3	99.7	51.1
24	75.2	100.4	75.8
30	84.7	101.5	88.5

I hereby declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectively submitted,

Diane L Peterson, PhD

Marion Merrell Dow, Inc
Marion Park Drive
Kansas City, Missouri 64137
September 29, 1993

MAIL ROOM JUL 26 1993 PAT. & TRADEMARK 30

RECEIVED GROUP 150
JUL 30 1993

PATENT

#9 8/4/93

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Hendrickson
Serial No.: 07/872,572
Filed: 04/23/92
Title: DILTIAZEM FORMULATION

Examiner: Benston Jr. W.
Art Unit: 1502

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C., 20231, on

7-21-93
(Date of Deposit)

R. A. Kell
Signature

DECLARATION UNDER 37 C.F.R. 1.132

The Honorable Commissioner
of Patents and Trademarks
Washington, D.C., 20231
Sir:

I Vijay O. Bhargava, PhD. do hereby declare that:

I obtained a Bachelor of Science in Pharmacy from Bombay University at Bombay India in 1979. I obtained a PhD. in Pharmacokinetics & Biopharmaceutics from Virginia Commonwealth University located in Richmond Virginia in 1984. From December of 1984 until June of 1988, I was employed by the University of Nebraska Medical Center as an assistant professor. My responsibilities included teaching pharmacokinetics and biopharmaceutics, as well as directing the research activities of graduate students.

From July of 1988 until the present, I have been employed by Marion Merrell Dow and its predecessor Marion Labs (hereinafter MMD). My responsibilities have included designing, analyzing and supervising clinical studies designed to evaluate the pharmacokinetic properties of new dosage forms.

The following clinical study was conducted under my supervision. The dosage form utilized in the study was prepared in the same manner as disclosed in Example 3 of United States

Patent application serial number 872,572. Two (2) of these 120mg diltiazem capsules were administered simultaneously in order to produce a final dosage of 240mg/day of diltiazem.

The study was carried out using twenty four (24) healthy male volunteers ranging in age from 19-45 years old. These volunteers were administered 240 mg/day of diltiazem on 7 successive days utilizing the dosage form described immediately above. Twenty-two volunteers completed the study.

Blood (plasma) samples were collected just prior to the 1st dose. Additional samples were obtained as follows: - just prior to the 6th dose, just prior to the 7th dose and 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, and 30 hours after the 7th dose.

Plasma concentrations of the diltiazem and metabolites were determined by HPLC analysis. Model-independent pharmacokinetic data analysis was performed on the resultant plasma diltiazem concentration - time data. The mean plasma concentrations are listed below in Table I (value in parenthesis represents % CV).

TABLE I INVENTION

Time 6th Dose:	Diltiazem Mean Plasma Concentration (ng/ml) (% CV)	
0 hours	63.11	(39.5)
7th dose		
0 hours	73.20	(36.7)
2 hours	67.48	(37.3)
4 hours	80.51	(37.8)
6 hours	121.91	(43.3)
8 hours	133.30	(33.0)
10 hours	113.93	(40.0)
12 hours	105.81	(42.0)
14 hours	105.45	(47.6)
16 hours	104.39	(46.6)
18 hours	92.27	(45.2)
20 hours	77.56	(41.2)
22 hours	68.47	(39.8)
24 hours	63.22	(40.2)
26 hours	57.34	(36.8)
28 hours	51.13	(40.4)
30 hours	40.55	(48.7)

The Mean values for the following pharmacokinetic parameters were determined from the plasma concentration time profiles: AUC- Area under the curve, Cmax- Maximum plasma concentration, Trough - minimum plasma concentration, Ratio- ratio of C-max to C-min, Tmax - time to maximum concentration. These mean values are reported below in Table II (value in parenthesis represents % CV).

TABLE II INVENTION

AUC (0-24 hr) (ng/mlxhr)	2288 (841)
CMAX ng/ml	146 (50)
RATIO (CMAX/CMIN)	2.7 (2.7)
TMAX (hr)	7.9 (2.1)
TROUGH (CMIN) (ng/ml)	66.5 (37)

I have reviewed the attached declaration of Dr. Weir describing the pharmacokinetic properties of the two Elan formulations and compared the results with those obtained with the formulation of the instant invention. It is my opinion that the formulation of the instant invention is superior to those described by the '240 patent. The reason for this superiority is based upon the substantially higher trough levels provided by the formulation of the instant invention when compared with that obtained by the Elan formulations.

The trough level is the plasma concentration of drug that is achieved by a given formulation immediately prior to the scheduled administration of the next dose. A good sustained release product provides trough plasma concentrations that may be comparable to those obtained when the product may be given in divided doses 3 to 4 times a day. If this quality is lacking the patient may be acheiving sub-therapeutic trough levels and may lack efficacy over part of the dosing period.

The trough levels obtained with the two Elan formulations, the 60mg tablets administered 4 times daily and the formulation of the instant invention are presented immediately below for the Examiner's convenience:

MEAN TROUGH LEVELS

TREATMENT	TROUGH LEVEL ng/ml
Elan A	48.5
Elan B	46.0
60 mg qid	67.3
Invention	66.5

The trough levels produced by the two Elan formulations are approximately 30% below that produced by the formulation of the instant invention. The significantly lower level of drug may correspond to a decreased therapeutic effect over the relevant portion of the dosing period.

Another advantage of the formulation of the instant invention is how closely the trough levels correspond to those obtained with the 60mg tablets administered 4 times daily. This will facilitate the conversion of the patient from a dosage form requiring administration 4 times daily to the convenience of a once a day dosage form.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Vijay Bhargava

Vijay C. Bhargava

Marion Merrell Dow Inc.
2110 E. Galbraith Road
Cincinnati, Ohio 45215

MAIL ROOM JUL 26 1993 30 PAT. & TRADEMARK OFF.

JUL 30 1993

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	Examiner: Benston Jr. W
Hendrickson et al.	)	Art Unit: 1502
Serial No.: 07/872,572	)	
Filed: 04/23/92	)	
Title: Diltiazem Formulation	)	
	)	

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C., 20231, on

7-21-93
(Date of Deposit)

R.A. Kell
Signature

DECLARATION UNDER 37 C.F.R. 1.132

The Honorable Commissioner
of Patents and Trademarks
Washington, D.C., 20231

Sir:

I, Scott Weir, Pharm.D. PhD. do hereby declare that:

I obtained the following degrees from the University of Nebraska: A Bachelors of Science in Biology in 1977, a Pharm.D. in 1980 and a Ph.D. in Pharmacokinetics and Biopharmaceutics in 1986.

From March of 1986 until the present, I have been employed by Marion Merrell Dow and its predecessor Marion Labs (hereinafter MMD). I am currently the Department Head of the US Clinical Pharmacokinetics Department responsible for supervising associates employed within the department and establishing departmental goals and procedures. My department's activities include designing, analyzing and supervising clinical trials designed to characterize the pharmacokinetics, pharmacodynamics and metabolism of new chemical entities as well as to evaluate the biopharmaceutic properties of new dosage forms. Previously, I was employed in the department as a pharmacokineticist responsible for directly carrying out the activities described above.

The following clinical study was carried out under my supervision. This study was designed to determine the biopharmaceutic properties of once-a-day diltiazem dosage forms

utilizing diltiazem pellets having dissolution profiles corresponding to those specified in United States Patent No. 4,894,240 (hereinafter the '240 patent).

Two diltiazem formulations, corresponding to those described by the '240 patent, were obtained from Elan Corporation Plc. of Althone Ireland for biopharmaceutic evaluation as potential once-a-day products. Each formulation contained 240 mg of diltiazem. As is described by the '240 patent, the formulation was a blend of two types of pellets. One type of pellet had been coated with a polymer to provide a sustained release of diltiazem (hereinafter sustained release). The other type of pellet was not coated thereby providing for the immediate release of diltiazem (hereinafter immediate release). These pellets had the following composition:

DILTIAZEM SUSTAINED RELEASE BEADS

COMPONENT	AMOUNT (expressed as mg/g of pellets)
Diltiazem HCl	384.3
Fumaric Acid	96.1
Talc	365.2
Sugar Spheres	96.1
Eudragit RS 12.5	26.2
Eudragit RL 12.5	6.5
Povidone	25.6

DILTIAZEM IMMEDIATE RELEASE PELLETS

COMPONENT	AMOUNT (expressed as mg/g of pellets)
Diltiazem HCl	600
Fumaric Acid	150
Talc	60
Povidone	40
Sugar Spheres	150

One formulation contained 10w/w% of the immediate release pellets and 90w/w% of the sustained release pellets (hereinafter Elan Formulation A). The second formulation contained 15 w/w% of the immediate release pellets and 85 w/w% of the sustained release pellets (hereinafter Elan Formulation B).

The dissolution profiles of each of these formulations was evaluated in 0.05M KCL as described in the '240 patent beginning at line 65, column 2. This dissolution testing was carried out at Elan's facilities by Elan personnel and the results were provided to MMD.

Elan formulation A exhibited the following dissolution profile:

DISSOLUTION PROFILE

TIME	% DILTIAZEM HCL RELEASED
2 Hr	12.2
4 Hr	18.1
6 Hr	34.2
8 Hr	50.8
10 Hr	64.4
13 Hr	79.7
24 Hr	97.6

Elan formulation B exhibited the following dissolution profile:

DISSOLUTION PROFILE

TIME	% DILTIAZEM HCL RELEASED
2 Hr	14.7
4 Hr	21.5
6 Hr	36.9
8 Hr	53.8
10 Hr	69.0
13 Hr	82.5
24 Hr	102.2

The pharmacokinetic profile of the two Elan formulations was determined in the following study. Twenty-four healthy male volunteers participated in the study. The volunteers ranged in age from 19 to 45 years old. No participants body weight varied by more than 10% from the ideal body weight for that individual. Each of the volunteers participated in the following randomized, three way crossover study design.

The following three dosage regimens were utilized. In one dosage regimen, the volunteers received one dose of Elan Formulation A daily for seven days (240mg/day of diltiazem HCl). In another dosage regimen, volunteers received one dose daily of the Elan B formulation for seven days (240mg/day of diltiazem HCl). As a reference formulation the volunteers were administered 60 mg of diltiazem HCl, via non-sustained release tablets, 4 times daily, for 1 week (28 doses). Tablets available commercially from Marion Labs under the trade name Cardizem® were utilized.

Blood (plasma) samples were drawn from the volunteers according to the following schedule. When the volunteers were receiving either of the Elan formulations, samples were drawn on day 7 just prior to the administration of the last dose and 2, 4, 6, 7, 10, 12, 14, 16, 18, 20, 22, 24, and 30 hours after the last dose. In addition, a trough blood level was obtained on day 6 by obtaining a sample just prior to the administration of the 6th dose. For volunteers receiving the 60 mg tabs, the samples were drawn just prior to the administration of the 21st and 25th doses and 1, 2, 3, 4, and 6 hours after the 25th dose. The same protocol was followed with the 26th, 27th and 28th doses except that a sample was also drawn 12 hours after the administration of the 28th dose. Additionally, pre-dose samples were obtained prior to administration of the first dose on day 1 for all three dosage regimens.

Plasma concentrations of the diltiazem were determined by HPLC analysis. Model-independent pharmacokinetic data analysis was performed on the resultant plasma diltiazem concentration - time data. The mean plasma concentrations for the relevant time period is reported below. Table I reports the values obtained

for Elan Formulation A (% CV represents coefficent of variation). Table II reports the values obtained for Elan formulation B. Table III reports the values obtained with the 60 mg Cardizem® marketed tablets.

TABLE I ELAN FORMULATION A

Time	Diltiazem Mean Plasma Concentration (ng/ml) (% CV)	
6th Dose:		
0 hours	49.31	(31.28%)
7th dose		
0 hours	48.62	(31.02%)
2 hours	75.04	(36.64%)
4 hours	65.89	(37.53%)
6 hours	63.92	(36.31%)
7 hours	71.32	(37.11%)
10 hours	98.14	(27.59%)
12 hours	104.24	(25.86%)
14 hours	95.92	(26.10%)
16 hours	84.99	(23.44%)
18 hours	75.94	(25.34%)
20 hours	61.89	(23.78%)
22 hours	53.34	(25.37%)
24 hours	47.70	(25.85%)
30 hours	28.50	(30.07%)

TABLE II ELAN FORMULATION B

Time 6th Dose:	Diltiazem Mean Plasma Concentration (ng/ml) (% CV)	
0 hours	47.73	(36.84%)
7th dose		
0 hours	47.15	(33.84%)
2 hours	94.52	(27.55%)
4 hours	77.13	(31.83%)
6 hours	69.78	(33.79%)
7 hours	70.15	(31.41%)
10 hours	91.36	(29.85%)
12 hours	94.97	(29.27%)
14 hours	84.36	(25.43%)
16 hours	78.47	(27.43%)
18 hours	69.00	(25.20%)
20 hours	56.63	(26.07%)
22 hours	48.57	(25.20%)
24 hours	43.05	(24.63%)
30 hours	27.75	(37.10%)

TABLE III Cardizem Tablets

Time 21st Dose:	Diltiazem MeanPlasma Concentration (ng/ml) (%CV)	
0 hour	71.31	(28.42%)
25th dose		
0 hour	66.47	(30.79%)
1 hour	86.19	(29.73%)
2 hours	107.98	(27.01%)
3 hours	127.01	(24.28%)
4 hours	108.94	(26.40%)
6 hours	73.11	(25.60%)
26th dose		
1 hour	82.15	(25.82%)
2 hours	105.69	(28.46%)
3 hours	110.13	(23.39%)
4 hours	94.10	(21.72%)
6 hours	61.90	(26.95%)
27th dose		
1 hour	58.29	(30.48%)
2 hours	79.66	(28.42%)
3 hours	93.11	(26.33%)
4 hours	77.48	(25.04%)
6 hours	55.05	(24.25%)
28th dose		
1 hour	60.26	(37.97%)
2 hours	64.96	(36.89%)
3 hours	70.69	(31.47%)
4 hours	73.61	(26.37%)
6 hours	64.19	(25.97%)
12 hours	24.94	(33.39%)

The Mean values for the following pharmacokinetic parameters were determined from the plasma diltiazem concentration time profiles: AUC- Area under the curve, Cmax- Maximum steady-state plasma concentration, Trough - average of 7 AM plasma concentrations obtained prior to dosing on days 6 and 7 in addition to 24 hours post-dose on day 8, Ratio- ratio of C-max to C-min, the minimum steady state plasma concentration, Tmax - time to maximum concentration. These mean values are reported below in Table IV (Value in parenthesis represents % CV).

TABLE IV

	Tablet 60 mg qid	Elan A 240 mg/ day	Elan B 240 mg/ day
AUC (0-24 hr) (ng/mlxhr)	1960 (23)	1801 (26)	1760 (26)
CMAX (ng/ml)	129 (23)	108 (26)	106 (27)
RATIO (CMAX/CMIN)	2.8 (17)	2.5 (20)	2.6 (15)
TMAX (hr)	4.0 (57)	11.8 (22)	8.1 (62)
TROUGH (ng/ml)	67.3 (26)	48.5 (27)	46.0 (29)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Scott Weir

Scott Weir

Marion Merrell Dow Inc.
2110 E. Galbraith Road
Cincinnati, Ohio 45215

Schedule "D"

(Data)

Subj #	DILTIAZEM HCl ER CAPSULES, 300 mg					CARDIZEM CD CAPSULES, 300 mg				
	AUC0-t (ng.h/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Tmax (h)	Deg (%)	AUC0-t (ng.h/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Tmax (h)	Deg (%)
1	2078.572	151.41	26.48	11	144.249	1447.29	171.9	14.59	6	260.8627
2	1359.234	110.69	13.25	5.517	172.0498	4041.132	240.44	71.2	14	100.5105
3	3477.393	198.42	57.31	8	97.3902	5116.295	248.46	88.35	6.5	75.10591
4	3091.895	139.75	43.5	6	74.71146	2669.537	162.6	45.7	5.5	105.0969
5	2577.773	130.06	42.51	15	81.51222	2465.813	172.69	27.17	5.5	141.636
6	2141.346	117.82	37.96	12	89.50632	2685.24	148.79	45.21	5.5	92.5772
7	4788.774	205.87	95.69	5.5	55.21914	5626.248	298.56	112.93	5	79.18456
8	6777.613	525.3	56.67	10	165.9451	3719.162	222.73	53.03	5.5	109.5085
10	3946.338	180.08	76.72	6	62.85929	4126.243	255.38	89.89	5	96.25609
11	12068.75	559.33	218.31	8	67.8155	12139.63	625.64	245.78	5	75.09818
12	4606.11	221.64	95.67	12	65.6363	3241.001	158.23	55.58	6	76.01355
14	4126.35	218.26	59.45	5.5	92.36832	4303.359	274.71	81.3	6	107.8655
15	5236.055	244.16	88.24	6	71.46755	5838.87	303.66	102.62	5.5	82.63517
16	5634.588	377.21	92.59	7	121.2312	4682.739	249.09	66.08	2	93.79639
18	3345.884	146.01	66.92	7	56.7312	3671.29	210.79	79.1	6	86.08854
19	2881.342	152.24	34.91	14	97.72948	2638.127	138.22	48.74	6	81.40321
20	4871.86	300.22	84.71	8	106.1656	4483.848	197.83	96.53	6.5	54.46422
21	2586.06	125.33	47.49	8	72.23906	2379.925	130.48	40.85	5	90.38604
22	4364	196.62	83.34	6.5	62.29881	3826.998	212.28	72.45	6.5	87.69067
23	3498.76	174.3	51.62	10	84.15324	6569.733	362.07	107.26	5	93.08506
24	6290.76	268.56	115.16	14	58.52393	5606.891	535.56	72.72	5	198.1162
25	4421.907	191.87	58.84	7	72.20233	4726.193	232.4	70.29	5.5	82.3206
26	2872.368	168.79	34.09	9	112.5483	2654.657	177.53	39.76	5.5	124.5539
27	2748.773	141.1	49.1	6	80.32675	2720.97	171.67	41.9	5.5	114.4621
28	4051.398	215.28	66.56	8	88.09996	4904.238	297.49	44.69	5	123.7134
29	2426.665	121.28	41.77	8	78.63632	2320.737	135.53	37.62	5	101.254
30	5609.233	305.55	89.66	14	92.37199	3824.683	261.7	62.12	5	125.237
31	4274.235	177.14	85.28	15	51.57976	3482.658	167.16	82.5	5	72.12422
32	8306.812	295.96	186.78	5.5	31.54423	9592.145	480.51	175.13	5	76.40752
33	8930.65	400.26	205.55	7	52.32587	6126.418	357.42	118.32	5.5	93.66648
34	4200.058	202.71	68.39	5.5	76.75323	5317.881	392.69	82.29	4.5	140.0859
36	3777.145	186.07	69.54	15	74.04323	3644.333	201.8	59.39	5.5	93.78506
38	2814.43	128.63	52.62	8	64.81739	3126.726	221.48	65.23	5.5	119.9338
39	5887.888	353.98	90.25	5.5	107.5007	4733.12	357.71	52.18	11	154.9236
40	2546.228	142.91	46.49	14	90.88267	2554.082	176.46	38.14	5	129.9755
Mean	4360.49	222.14	75.24	8.93	84.98	4313.95	255.76	73.33	5.76	106.85
SD	2182.38	109.59	46.14	3.30	39.46	2076.84	115.15	43.01	1.88	38.73
CV	49.59	49.34	61.32	36.97	35.85	48.14	45.02	58.66	32.73	36.24
Geo Mean	3939.58	202.15	64.65	8.39	80.24	3937.97	235.85	64.17	5.53	101.72

Schedule "E"

(Article by Eradiri, O. et al., entitled
"Comparison of diltiazem bioavailability from 3 marketed extended-release products for once-daily administration: implications of chronopharmacokinetics and dynamics",
International Journal of Clinical Pharmacology and Therapeutics, (1997), Vol. 35, No. 9, p. 369-373)

International Journal of Clinical Pharmacology and Therapeutics, Vol. 35, No. 9 – 1997 (369–373)

Comparison of diltiazem bioavailability from 3 marketed extended-release products for once-daily administration: implications of chronopharmacokinetics and dynamics

O. Eradiri[1] and K.K. Midha[2]

[1]*Research and Development Division, Biovail Corporation International, Mississauga, Ontario, Canada, and* [2]*Drug Metabolism, Drug Disposition Group, College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan, Canada*

Abstract. Diltiazem has proven to be an effective antihypertensive and antianginal agent, due to its potent calcium channel blocking activity. The present study was conducted to compare the bioavailability of a new extended release diltiazem HCl capsule formulation (Tiazac) with 2 other currently marketed products (Cardizem CD and Dilacor XR). Fourteen healthy male subjects participated in this randomized, 3-period, multiple daily dose (240 mg for 7 days), crossover bioavailability study. ANOVA and multiple comparison tests showed the parent drug $AUC_{0-\tau}$ to be significantly higher after daily dosing with Tiazac than with the other 2 marketed products, but the diltiazem C_{min} values were not significantly different between the 3 formulations. Between 5 and 12 hours after drug administration, mean plasma diltiazem levels for Tiazac capsules were found to be significantly higher than those of the 2 other products tested. Comparison of plasma concentrations of metabolites for the 3 capsule formulations by ANOVA and multiple comparison tests showed similar trends as in the case of parent drug concentrations. These findings may be clinically important as higher and more consistent plasma concentrations of diltiazem, and its active metabolite during daytime are needed to counteract higher blood pressures in hypertensive patients due to circadian variations. The new extended release product of diltiazem HCl was found to exhibit significantly differing pharmacokinetics of the parent compound compared to either of the other 2 products tested.

Key words: bioavailability – diltiazem – clinical significance – controlled release – pharmacokinetics

Introduction

Diltiazem is a potent calcium channel blocker and its role in the management of essential hypertension is well established [Oates 1996]. While the drug is readily absorbed, it exhibits low bioavailability and short half-life due to substantial first-pass metabolism [Herman et al. 1983]. On account of these pharmacokinetic properties, all immediate release diltiazem HCl products are considered short-acting because patients generally have to ingest them 3 – 4 times a day to effect adequate blood pressure control. Twice-and once-a-day extended release diltiazem formulations have been available for several years. A major advantage of extended release formulations of the drug is optimization of antihypertensive therapy by improving patient compliance and safety, the latter through elimination of multiple peaks in plasma diltiazem concentrations due to 3- to 4-times-a-day-dosing of immediate release formulations. Tiazac is a new extended release capsule formulation of diltiazem hydrochloride for once-a-day dosing, which recently became available in the United States and Canada. This study was conducted during the clinical development of Tiazac capsules to compare its pharmacokinetic profile with those of 2 other FDA-approved drug products, Cardizem CD and Dilacor XR, capsules. In this report, comparison of pharmacokinetic profiles of 3 drug products and their clinical implications are discussed.

Received July 4, 1997.

Correspondence to Dr. O. Eradiri, Research and Development Division, Biovail Corporation International, 2488 Dunwin Drive, Mississauga, Ontario, Canada L5L 1J9.

Methods, materials, and subjects

The protocol was approved by the Institutional Review Board of the Contract Research Organization where the study was conducted. Fourteen healthy male volunteers

with ages ranging from 21 – 37 years and weighing 55 – 95 kg were admitted into the study. Written informed consents were obtained from the volunteers. The new formulation (240 mg Tiazac capsules-marketed in Canada and the USA by Crystaal Corporation and Forest Labs Inc., respectively-, Biovail Corporation International), is a multiparticulate system consisting of polymer-coated beads in hard gelatin capsules. The 2 other formulations were 240 mg Cardizem CD capsules (Marion Laboratories) and 240 mg Dilacor XR capsules (Rhone-Poulenc Rorer). Each of these 3 formulations was administered once daily over a 7-day study period in a crossover design. Each subject received all 3 formulations; the formulation sequences for individual subjects were assigned according to a randomization schedule. There was a 1-week washout period between drug administrations.

In each period subjects were institutionalized in the clinic the evening prior to drug administration. They fasted from 10 p.m. the evening prior to dosing until specified meal times. Dosing was at 7 a.m. daily and the subjects ingested the assigned formulation with 240 ml of water. On days 1 through 6 of each dosing period, standardized, caffeine-free meals were ingested by the subjects at 9:30 a.m., 1 p.m., 6 p.m., and 10 p.m. On day 7 of each study period, meals were provided at 11:30 a.m., 4:30 p.m., and 10 p.m. Vital signs and ECGs were monitored at predetermined times throughout the study.

On day 1, and days 4 through 7, a pre-dose blood sample (10 ml each) was collected at 7 a.m. Post-dose steady-state blood samples (10 ml each) on day 7 were collected at 1, 2, 3, 4, 5 6, 7, 8, 10, 12, 16, 20, and 24 hours. Precooled EDTA vacutainers were used for blood sample collection. All blood samples were centrifuged within 15 minutes of collection and the plasma portions were harvested, frozen, and stored at –70° C until analysis. A validated HPLC procedure [Eradiri and Midha 1995] was used in the analysis of the plasma samples for levels of diltiazem (DTZ) and its 2 major metabolites, desacetyldiltiazem (DEA) and N-desmethyldiltiazem (DEM). The calibration ranges for DTZ, DEA, and DEM were 3 – 800, 1 – 200, and 3 – 700 ng/ml, respectively. Interday coefficients of variation for the lower limits of quantitation were 9.5%, 8%, and 10.4% for DTZ, DEA, and DEM, respectively. Intra- and interassay precisions of the method were less than 5% for all 3 analytes.

The areas under the plasma concentration versus time curves ($AUC_{0-\tau}$) were calculated using the linear trapezoidal method. The maximum analyte plasma concentrations (C_{max}), minimum plasma concentrations (C_{min}) and the time to attain C_{max} (t_{max}) were taken directly from the raw data. The degree of fluctuation was calculated using the formula: $100 \times ((C_{max} - C_{min})/(AUC_{0-\tau/24}))$. The predose plasma concentrations for all 3 analytes on days 4 through 7 were tested for differences (ANOVA) to determine if steady-state was attained. ANOVAs were also performed on plasma concentrations for all 3 analytes at protocol-specified sampling time points to determine formulation differences, if any. The pharmacokinetic parameters of Tiazac were compared with those of the 2 formulations tested for all 3 analytes by ANOVA at the 5% level of significance using SAS General Linear Model Procedure. Geometric 90% confidence intervals calculated using the two 1-sided test procedure [Schuirmann 1987] were determined for $AUC_{0-\tau}$, C_{max}, and C_{min} ratios between the new formulation and each of the 2 other formulations. Confidence intervals for ratios falling outside 0.80 – 1.25 were deemed bioinequivalent. In cases, where ANOVA detected significant differences, the Duncan's multiple comparison test was performed.

Results

All 14 subjects completed the study in its entirety. ANOVA of each product's predose C_{min} values on days 4 through 7 for all 3 analytes (DTZ, DEA, and DEM) did not reveal any differences; this outcome indicated steady-state was achieved in each case.

The mean steady-state plasma DTZ, DEA, and DEM concentration versus time curves on day 7 for all 3 extended release formulations are presented in Figure 1. Plasma diltiazem concentrations for all 3 formulations gradually increased after morning dosing to peak concentrations which occurred between 5 and 7 hours, upon reaching C_{max}, higher levels of plasma diltiazem were maintained longer after Tiazac relative to Cardizem CD and Dilacor XR. In addition, Tiazac consistently provided significantly higher plasma diltiazem concentrations from hour 5 to hour 12 when compared to either of the other 2 products (Table 1). There were no statistically significant differences among the plasma diltiazem concentrations exhibited by the 3 formulations between 20 and 24 h post dose. Plasma concentration versus time curves for the 2 metabolites showed similar trends. The plasma DEA concentrations following Tiazac administration were significantly higher than those of Cardizem CD and Dilacor XR at 6, 7, 8, 9, 10, and 12 h. In the case of DEM, significantly higher plasma levels due to Tiazac capsules were observed at 5, 6, 7, and 12 h.

Table 2 presents a summary of the means of pertinent pharmacokinetic parameters for the 3 formulations. For the parent drug, Tiazac demonstrated significantly higher $AUC_{0-\tau}$ (> 20%) than either of the 2 other marketed products. While the steady-state diltiazem C_{min} values for all 3 formulations were not different, Tiazac had a significantly higher (> 20% higher) diltiazem C_{max} value than either of the 2 other formulations tested. All 3 products exhibited similar degree of fluctuation of diltiazem plasma concentrations. The metabolites' pharmacokinetic parameters showed that Tiazac exhibited significantly greater mean DEA and DEM $AUC_{0-\tau}$ values than the other 2 formulations. While the DEA and DEM C_{max} values for Tiazac

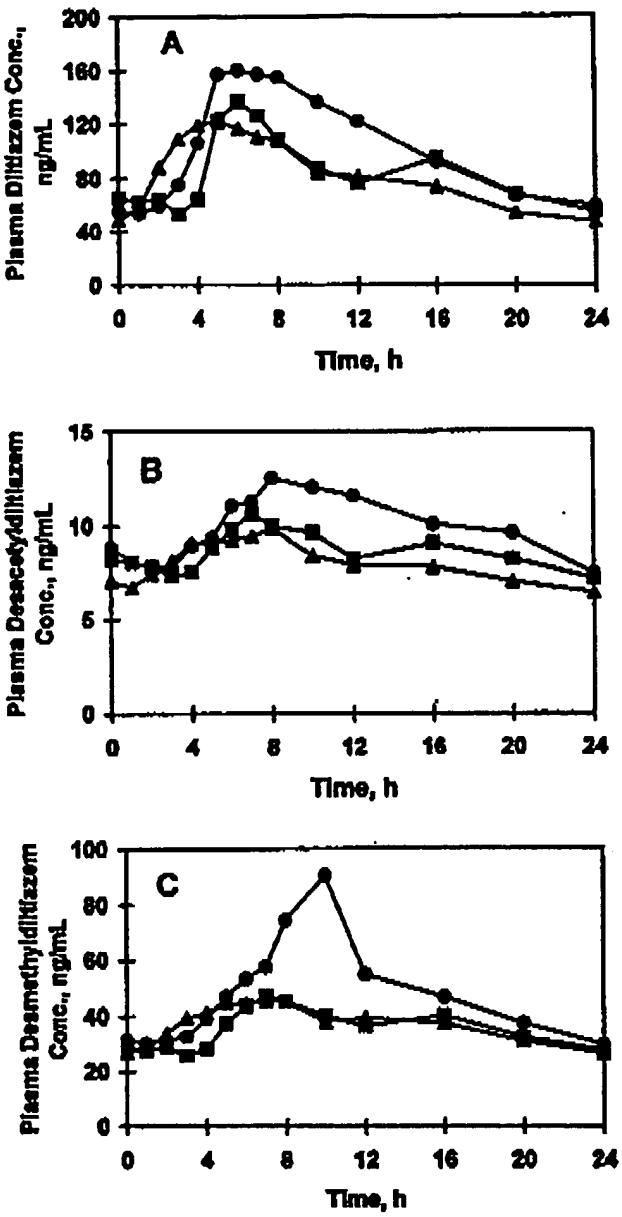


Fig. 1 Mean diltiazem (A), desacetyldiltiazem (B), N-desmethyldiltiazem (C) plasma concentration versus time curves on day 7 after daily doses of 3 different brands of 240 mg diltiazem extended-release formulation (Tiazac ●, Cardizem CD ■, and Dilacor XR (▲) in 14 healthy male volunteers. (Tiazac is marketed in Canada and the United States by Crystaal Corporation and Forest Labs Inc., respectively.)

were significantly higher than the corresponding C_{max} values for the 2 other formulations, the C_{min} values of both primary metabolites were not different for the 3 formulations.

The point estimates of key bioequivalence parameters of Tiazac (the test formulation) to those of the 2 other formulations (as references) are also presented in Table 2 for all 3 analytes. The 90% geometric confidence intervals

Table 1 Steady-state (mean ± SE) plasma diltiazem concentrations following daily administration of 240 mg diltiazem HCl for 7 days as 3 different extended release capsules to 14 healthy male volunteers.

Sampling time (h)	Tiazac	Cardizem CD	Dilacor XR	p value
0	55.1 ± 5.4	65.0 ± 8.4	48.3 ± 5.3	n.s.
	53.0 ± 5.8	61.7 ± 9.1	57.2 ± 6.7	n.s.
2*	58.7 ± 5.7^b	63.5 ± 8.3^b	87.9 ± 9.0^a	0.003
3*	74.1 ± 7.2^b	52.4 ± 6.4^c	108.6 ± 10.2^a	0.0001
4*	105.8 ± 11.5^a	62.8 ± 5.1^b	118.6 ± 9.7^a	0.0001
5*	156.9 ± 15.5^a	122.8 ± 14.6^b	121.0 ± 14.2^b	0.0382
6*	160.1 ± 11.5^a	136.4 ± 11.1^b	115.9 ± 11.1^c	0.0002
7*	156.8 ± 10.4^a	125.7 ± 11.8^b	109.5 ± 11.3^b	0.0009
8*	154.5 ± 9.1^a	107.5 ± 9.9^b	107.0± 11.6^b	0.0001
10*	135.7 ± 9.1^a	86.3 ± 7.2^b	82.4 ± 8.0^b	0.0001
12*	120.8 ± 9.2^a	74.6 ± 7.2^b	79.8 ± 7.3^b	0.0001
16*	90.7 ± 7.4^a	93.7 ± 9.2^a	72.1 ± 8.4^b	0.0234
20	65.6 ± 5.8	66.7 ± 6.2	52.9 ± 5.3	n.s.
24	58.2 ± 8.0	53.8 ± 5.3	46.7 ± 4.3	n.s.

* = $p < 0.05$ treatment means with different letters were significantly different (ANOVA followed by multiple comparison test)

for the parent drug and metabolites' $AUC_{0-\tau}$ comparisons consistently had statistical power > 0.80. Tiazac exhibited mean diltiazem $AUC_{0-\tau}$ which was 24% and 29% greater than the corresponding mean diltiazem $AUC_{0-\tau}$ values for Cardizem CD and Dilacor XR, respectively. The mean $AUC_{0-\tau}$'s of DEA and DEM for Tiazac were 18 – 29% greater than the corresponding values for the other 2 marketed products used in this study as references.

Discussion

Tiazac, the new extended release diltiazem HCl product for once daily administration, was found to provide 24 and 29% greater parent drug exposure in the present steady-state study than Cardizem CD or Dilacor XR, respectively. The outcomes with respect to the primary metabolites' AUC comparisons were similar to those of the parent drug. Tiazac is therefore bioinequivalent to either Cardizem CD or Dilacor XR. The analyses of peak exposure, i.e. C_{max} values and plasma drug levels, at individual sampling time points showed that the greater bioavailability with Tiazac could be attributed to higher concentrations of diltiazem and metabolites from hour 5 through hour 12 after daily dosing with the new extended release formulation.

Clinically it is of interest to examine the significance of the observed differences in bioavailability of diltiazem from the 3 extended release products. It is noted that the shapes of the plasma concentration versus time profiles for diltiazem and its 2 primary metabolites after dosing of the new extended release formulation (Tiazac capsules) were markedly different from those of Cardizem CD and Dilacor XR (Figure 1). The plasma desacetyldiltiazem and N-des-

Table 2 Steady-state pharmacokinetic parameters of DTZ, DEA, and DEM following daily administration of 240 mg diltiazem hcl for 7 days as 3 different extended-release capsules to 14 healthy male volunteers.

Analyte	PK parameters	Formulation	Mean	Test/Ref Ratio‡, %
Diltiazem	$AUC_{0-\tau}$*† (ng×hr/ml)	Tiazac	2,345 (1413 – 3570)[a]	
		Cardizem CD	1,882 (1,128 – 3,174)[b]	124 (110 – 139)
		Dilacor XR	1,808 (1032 – 3417)[b]	129 (115 – 145)
	C_{max}*† (ng/ml)	Tiazac	178 (124 – 305)[a]	
		Cardizem CD	147 (98 – 218)[b]	121 (106 – 138)
		Dilacor XR	125 (79 – 222)[b]	142 (125 – 162)
	C_{min}† (ng/ml)	Tiazac	44 (25 – 75)	
		Cardizem CD	42 (22 – 86)	106 (86 – 131)
		Dilacor XR	40 (15 – 84)	110 (90 – 135)
	t_{max}* (hours)	Tiazac	7.0 ± 1.8[a]	
		Cardizem CD	5.4 ± 1.5[b]	
		Dilacor XR	5.4 ± 2.0[b]	
	Degree of fluctuation (%)	Tiazac	139 ± 36	
		Cardizem CD	134 ± 40	
		Dilacor XR	114 ± 38	
Desacetyldiltiazem**	$AUC_{0-\tau}$*† (ng hr/ml)	Tiazac	230 (152 – 427)[a]	
		Cardizem CD	196 (104 – 366)[b]	118 (107 – 131)
		Dilacor XR	179 (99 – 363)[b]	129 (117 – 143)
	C_{max}*† (ng/ml)	Tiazac	13.1 (9.4 – 21.9)[a]	
		Cardizem CD	10.7 (5.9 – 18.7)[b]	122 (108 – 137)
		Dilacor XR	10.1 (5.3 – 18.4)[b]	130 (115 – 146)
	C_{min}† (ng/ml)	Tiazac	6.4 (3.2 – 12.1)	
		Cardizem CD	5.9 (2.4 – 11.8)	108 (91 – 127)
		Dilacor XR	5.3 (3.2 – 11.4)	119 (100 – 141)
	t_{max} (hours)	Tiazac	8.6 ± 2.0	
		Cardizem CD	10.2 ± 4.6	
		Dilacor XR	7.4 ± 2.8	
N-Desmethyldiltiazem	$AUC_{0-\tau}$*† ng hr/ml)	Tiazac	1,064 (651 – 1,509)[a]	
		Cardizem CD	846 (605 – 1,143)[b]	125 (113 – 139)
		Dilacor XR	854 (477 – 1,314)[b]	129 (112 – 138)
	C_{max}*† (ng/ml)	Tiazac	74 (50 – 509)[a]	
		Cardizem CD	48 (31 – 68)[b]	151 (117 – 195)
		Dilacor XR	47 (26 – 81)[b]	154 (119 – 199)
	C_{min}† (ng/ml)	Tiazac	28 (17 – 40)	
		Cardizem CD	24 (14 – 39)	118 (102 – 136)
		Dilacor XR	24 (14 – 38)	118 (102 – 135)
	t_{max} (hours)	Tiazac	8.5 ± 2.1	
		Cardizem CD	7.9 ± 2.7	
		Dilacor XR	6.8 ± 3.4	

† = geometric means, numbers in parentheses are ranges, * = $p < 0.05$ treatment means with different letters were significantly different, ‡ numbers in parentheses are 90% geometric confidence intervals, t_{max} and degree of fluctuation are expressed as mean ± SD, ** n = 13

methyldiltiazem levels in the present study were approximately 10 and 40%, respectively, of the parent drug concentrations. To date, the role of these 2 metabolites in antihypertensive therapy has not been well established. While desacetyldiltiazem is 25 – 50% as active as the parent drug as a vasodilator, there is little information on the potency of N-desmethyldiltiazem. Nevertheless, the fact that Tiazac delivered sustained and greater plasma concentrations of the parent drug from hour 5 to hour 12 after dosing as compared to the other marketed once daily products, may be an important finding from a chronotherapeutic perspective.

Circadian fluctuations in the onset of acute cardiovascular disease have prompted researchers to examine the diurnal cycles of heart rate and blood pressures [Muller and Willich 1996]. Heart rate exhibits a sharp rise in the morning and stays elevated throughout the day; heart rate slows down substantially at night. There is an early morning rise

in heart rate at around 4 a.m. Blood pressure follows a similar pattern. Highest blood pressures are observed between 9 a.m. and late afternoon. The daytime blood pressures are 20 – 30 mmHg higher than the nighttime blood pressures. Hence, from a chronotherapeutic perspective, an extended release antihypertensive product which can deliver sustained high plasma drug levels throughout the day may be especially advantageous to patients during the day. Tiazac possesses a plasma diltiazem concentration versus time profile which is appealing and suited for chronotherapeutic aspects of hypertension. This observation has support from a pharmacokinetic-pharmacodynamic consideration. In a recent clinical efficacy study with this new extended release product [Lacourciere et al. 1995], increasing the dose of Tiazac was associated with proportional reduction in blood pressure ($r = 0.99$). Hence, it is reasonable to postulate that higher steady-state plasma diltiazem concentrations are likely to result in greater antihypertensive effect during the day when clinical benefit is most needed.

Diastolic and systolic blood pressures, heart rate, and PR intervals were measured at predetermined times in each phase of this study for safety reasons only. Since it is well known that diltiazem does not elicit significant pharmacodynamic responses in healthy volunteers [Guimont et al. 1993], the study was not designed to evaluate differences in hemodynamics between the drug products. The relationship between plasma diltiazem levels and pharmacodynamic effects are better investigated in a controlled clinical trial using hypertensive patients.

Conclusion

Tiazac, a new once-a-day extended release capsule formulation of diltiazem HCl, exhibited greater diltiazem bioavailability than either of the other 2 extended release formulations marketed for once daily dosing. The increase in diltiazem bioavailability with Tiazac was due to sustained higher plasma concentrations from hour 5 to hour 12 after dosing. From a chronotherapeutic perspective, this new once-a-day capsule formulation may offer an advantage over other such diltiazem products in the treatment of hypertension.

REFERENCES

Eradiri O, Midha KK 1995 Use of parent drug and metabolite data in bioavailability assessment of a novel diltiazem hydrochloride once-daily product. Pharm Res *12:* 2071-2074

Guimont S, Landriault H, Klischer K, Grace M, Lambert C, Caille G, Gossard D, Russell A, Raymond M, Hutchings E, Spenard J 1993 Comparative pharmacokinetics and pharmacodynamics of two marketed bid formulations of diltiazem in healthy volunteers. Biopharm Drug Dis *14:* 767-778

Herman P, Rodgers SD, Remones G et al 1983 Pharmacokinetics of diltiazem after intravenous and oral administration. Eur J Clin Pharmacol *24:* 349-352

Lacourciere Y, Poirier L, Lefebvre et al 1995 Clinical efficacy of forced titrated doses of diltiazem extended-release – A placebo-controlled study. Am J Hypertens *8:* 282-286

Muller JE, Willich SN 1996 Circadian variation in the onset of myocardial infarction and sudden cardiac death. In: *Willich SN, Muller JE (ed)* Triggering of Acute Coronary Syndromes. Kluwer Academic Publishers, Dordrecht, The Netherlands

Oates J 1996 Antihypertensive agents and the drug therapy of hypertension, In: *Hardman JG, Limbird LE (ed)* Goodman and Gilman's The Pharmacological Basis of Therapeutics. McGraw Hill, New York, pp 780-808

Schuirmann DJ 1987 A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokin Biopharm *15:* 657-680

Schedule "F"

(Family of Patent listing)

L2 ANSWER 1 OF 1 INPADOC COPYRIGHT 2001 EPO

PATENT FAMILY INFORMATION
AN 39702087 INPADOC

+----------PRAI----------+		+----------AI----------+	
US 1991-721396	A 19910626	AT 1992-914768	EP 19920625
		AU 1992-22430	A 19920625
		CA 1992-2111085	A 19920625
		DE 1992-69229949	A 19920625
		DK 1992-914768	A 19920625
		EP 1992-914768	A 19920625
		US 1991-721396	A 19910626
		WO 1992-CA290	A 19920625
US 1991-721396	A1 19910626	US 1994-311722	A 19940923
US 1993-68951	B1 19930528	US 1994-311722	A 19940923
US 1994-311722	A 19940923	US 1994-311722	A 19940923
WO 1992-CA290	A 19920625	AU 1992-22430	A 19920625
WO 1992-CA290	W 19920625	DE 1992-69229949	A 19920625
		DK 1992-914768	A 19920625
		EP 1992-914768	A 19920625

+----------AI----------+		+----------PI----------+	
AT 1992-914768	EP 19920625	AT 184196	E 19990915
AU 1992-22430	A 19920625	AU 9222430	A1 19930125
CA 1992-2111085	A 19920625	CA 2111085	AA 19930107
DE 1992-69229949	A 19920625	DE 69229949	C0 19991014
		DE 69229949	T2 20000309
DK 1992-914768	A 19920625	DK 591424	T3 19991220
EP 1992-914768	A 19920625	EP 591424	A1 19940413
		EP 591424	B1 19990908
US 1991-721396	A 19910626	**US 5288505**	A 19940222
US 1994-311722	A 19940923	**US 5529791**	A 19960625
WO 1992-CA290	A 19920625	**WO 9300093**	A1 19930107

6 priorities, 9 applications, 11 publications